TRANSMITTAL OF APPEAL BRIEF (Small Entity)	Docket No. 02940086CA

In Re Application Of: **Peart et al.**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
10/759,280	01/20/2004	J. Alstrum Acevedo	30743	1616	6861

Invention: **DELTA9 TETRAHYDROCANNABINOL (DELTA9 THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE**

COMMISSIONER FOR PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed on:

☒ Applicant claims small entity status. See 37 CFR 1.27

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Dated: **June 13, 2008**

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cc:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re patent application of	Confirmation No.: 6861
J. Peart et al.	Group Art Unit 1616
Serial No. 10/759,280	Examiner: Alstrum Acevedo, James Henry
Filed: January 20, 2004	

For: ***Δ^9 TETRAHYDROCANNABINOL (Δ^9 THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE***

MAIL STOP APPEAL BRIEF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37

Claims 43, 46-48, 50, 52-55, and 57-63 of this application have been finally rejected in the office action dated January 25, 2008. A Notice of Appeal was timely filed April 25, 2008. This brief is in furtherance of the Notice of Appeal.

This brief contains these items under the following headings and in the order set forth below, as required under 37 C.F.R. § 41.37:

I. REAL PARTY IN INTEREST

II. RELATED APPEALS AND INTERFERENCES

III. STATUS OF CLAIMS

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V. SUMMARY OF CLAIMED SUBJECT MATTER

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VIII. CLAIMS APPENDIX

IX. EVIDENCE APPENDIX

X. RELATED PROCEEDINGS APPENDIX

I. Real Party in Interest

The real party in interest in the appeal is:

- ☐ the party named in the caption of this brief.
- ☑ the following party (ies):

  Virginia Commonwealth University, which owns this application.

II. Related Appeals and Interferences

With respect to other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal:

☑ there are no such appeals or interferences.

☐ these are as follows:

III. STATUS OF CLAIMS

The status of the claims in this application is as follows:

A. Total number of claims in Application

The claims in the application are: Claims 43, 46-48, 50, 52-55, and 57-63

totaling 16 claims

B. Status of all the claims:

1. Claims cancelled: 1-42, 44-45, 49, 51, 56
2. Claims withdrawn from consideration but not cancelled: None
3. Claims pending: 43, 46-48, 50, 52-55, and 57-63
4. Claims allowed: None
5. Claims rejected: 43, 46-48, 50, 52-55, and 57-63
6. Claims objected to: None

C. Claims on Appeal.

The claims on appeal are: Claims 43, 46-48, 50, 52-55, and 57-63

IV. STATUS OF AMENDMENTS

The status of amendments is as follows: There is no unentered amendment.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed invention, defined in independent claim 57, 59, 61, 63 and in dependent claims 43, 46-48, 50, 52-55, 58, 60, 62, is directed to aerosolized tetrahydrocannabinol (THC) and aerosol-dispensable THC. Applicants were the first to aerosolize THC in a pharmaceutically useable form.

In one aspect, the invention is "[a]n aerosol-dispensable[1] pharmaceutical composition[2] comprising: tetrahydrocannabinol[3] and hydrofluoroalkane[4], wherein the composition is aerosol-dispensable." (Claim 57.)

In another aspect, the invention is "[a]n aerosolized[5] pharmaceutical composition comprising: respirable droplets[6] comprising a tetrahydrocannabinol." (Claim 59.)

In a further aspect, the invention is a "method of aerosolizing a tetrahydrocannabinol, comprising: dissolving a tetrahydrocannabinol in a hydrofluoroalkane[7] and forming a stable pharmaceutical composition[8]; aerosolizing the stable pharmaceutical composition into respirable droplets comprising the tetrahydrocannabinol." (Claim 61.)

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[1]See, e.g., Applicants' specification, page 11, line 10.

[2]See, e.g., Applicants' specification, page 11, lines 7, 10.

[3]See, e.g., Applicants' specification, page 10, lines 21; 23-24; page 11, lines 1, 3, 6-7.

[4]See, e.g., Applicants' specification at page 11, lines 6-7.

[5]See, e.g., Applicants' specification at page 5, line 6 after the table; page 9, lines 17, 25; page 10, lines 2, 9; page 15, last line; page 19, last line; page 20, line 2; page 21, last line; page 24, line 12.

[6]See, e.g., Applicants' specification at page 14, line 2; Applicants' specification at page 27, line 1 of text.

[7]See, e.g., Applicants' specification at page 11, line 6.

[8]See, e.g., Applicants' specification at page 11, lines 6+.

Also in another aspect, the invention is a "non-CFC[9] aerosol-dispensable pharmaceutical composition comprising tetrahydrocannabinol (THC)." (Claim 63.)

[9]See, e.g., Applicants' specification at page 9, line 22; page 10, line 16.

VI. Grounds of Rejection to be Reviewed on Appeal

The issues presented in this Appeal are:

Whether Claims 43,46-48, 50, 53-55, **57**-58, **59**-60, **61**-62, **63** are unpatentable under 35 U.S.C. 103(a) based on Mechoulam et al. (U.S. Patent No. 5,804,592) ("Mechoulam") or Volicer (U.S. Patent No. 5.804,592) ("Volicer") in view of McNally et al. (U.S. Patent No. 5,653,961) ("McNally").

Whether Claims 43, 48, 50, 52-55, **57**-58, **59**-60, **61**-62, **63** are unpatentable over a combination of Pars and McNally.

ARGUMENT VIIA. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

There are no rejections under 35 U.S.C. §112, first paragraph.

ARGUMENT VIIB. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

There are no rejections under 35 U.S.C. §112, second paragraph.

ARGUMENT VIIC. REJECTIONS UNDER 35 U.S.C. §102

There are no rejections under 35 U.S.C. §102.

A. The Obviousness Rejection of Aerosolizing Method Claim 61 Over Mechoulam or Volicer in view of McNally; and The Obviousness Rejection Over Pars in view of McNally

Claim 61 recites a method of aerosolizing a THC, comprising dissolving a THC in an HFA and forming a stable pharmaceutical composition; and aerosolizing the stable pharmaceutical composition into respirable droplets comprising the THC.

There is no disclosure in either Mechoulam or Volicer (nor in McNally) of a step of dissolving THC in an HFA, nor of a step of forming a stable pharmaceutical composition from THC dissolved in HFA. There is no disclosure in either Mechoulam or Volicer (nor in McNally) of a step of aerosolizing a stable pharmaceutical composition into respirable droplets comprising THC. Each primary reference discloses <u>none</u> of the claimed method steps of Claim 61. McNally discloses <u>none</u> of the claimed method steps of Claim 61. The claimed invention of Claim 61 is quite removed from any of Mechoulam, Volicer, or McNally.

Pars is no closer than Mechoulam or Volicer. None of the Pars examples are aerosols. There is no disclosure in Pars of dissolving THC in an HFA, nor of a step of forming a stable pharmaceutical composition from THC dissolved in HFA. There is no disclosure in Pars of a step of aerosolizing a stable pharmaceutical composition into respirable droplets comprising THC. Pars discloses <u>none</u> of the claimed method steps of Claim 61.

There is no combination of Mechoulam, Volicer, Pars and McNally from which a person of ordinary skill in the art arrives at the invention of Claim 61. McNally, the secondary reference, does not even relate to THC but rather to a different drug, Butixocort Propionate. The uncontradicted evidence of record establishes how different Butixocort Propionate and THC are.

The obviousness rejections of Claim 61 should not be maintained.

B. Factual Findings Which Should Be Made

Regarding Dr. Joanne Peart's 30-paragraph Declaration Under 1.132 executed November 6, 2007 and the references attached thereto, the Examiner has not disagreed with a single statement therein. Presumably the Examiner admits the truth of all matters in Dr. Peart's Declaration otherwise he would have stated any disagreement.

For clarity of the record, and referring to the 1.132 Declarations of record in this application as well as Applicants' specification, there should be made expressly of record factual findings, including but not limited to the Examiner expressly making factual findings that:

1) As of the filing of the application, there was no pharmaceutically acceptable aerosol form of Δ^9 THC.[10]

2) In Mechoulam, Volicer, Pars and McNally (the four references on which the obviousness rejections are based), there is not one <u>actual example</u> of a THC aerosol.

3) In the four references on which the obviousness rejections are based, the only actual example of an aerosol is the Butixocort Propionate aerosol in McNally.

4) The structures of THC and Butixocort Propionate substantially differ.[11]

5) The solubility of THC cannot be inferred from the solubility of Butixocort Propionate.

6) THC and Butixocort Propionate cannot be considered interchangeable by a person of ordinary skill in the art for purposes of aerosol formulation.[12]

7) The properties of THC are unlike the properties of drugs that

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[10]Applicants' specification, page 9, line 4.

[11]Peart Declaration, paragraph 19.

[12]Peart Declaration, paragraphs 14, 18.

generally have been formulated into aerosols.[13]

8) The difficulty of working with THC was well documented in the literature.[14]

9) The large dosage amounts of THC required for systemic administration of THC were well documented in the literature.[15]

10) The properties of THC that make it unlike, and not interchangeable with, other drugs were well documented in the literature.[16]

11) THC was known to resemble rubber-cement rather than a powder.[17]

12) Most drugs resemble a powder, not rubber-cement. [18]

13) A further known difficulty in working with THC was the inability to grind THC (a resinous material) into a microfine powder.[19]

14) In formulations that contain drug substance suspended in propellant usually the drug is ground to a microfine powder before incorporation into the propellant mixture, but THC as a resinous material cannot be ground into a microfine powder.[20]

15) A person of ordinary skill in the art would not view THC as sufficiently soluble or stable to be used in a formulation to achieve necessary

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[13]Peart Declaration, paragraph 14.

[14]Peart Declaration, paragraph 14.

[15]Peart Declaration, paragraph 14.

[16]Peart Declaration, paragraph 14.

[17]Peart Declaration, paragraph 14.

[18]Peart Declaration, paragraph 14.

[19]Peart Declaration, paragraph 14.

[20]Peart Declaration, paragraphs 15-16.

metered and respirable doses.[21]

16) There is no prior art in which THC was formulated with HFA.

17) There is no prior art in which THC was dissolved in HFA.

18) There is no prior art in which a THC aerosol was formulated without CFC.

19) There is no prior art in which respirable droplets of THC were formulated without CFC.

20) A THC-CFC-ethanol formulation having 23% ethanol would fail to produce respirable particles.[22]

21) Before Applicants' invention, a person of ordinary skill in the art lacked knowledge of how to aerosolize THC without CFC.

22) Interest in pharmaceutical THC dates back ~ 30 years.[23]

23) Applicants were the first to formulate a non-CFC THC aerosol.

24) The Mechoulam actual example.is not an aerosol.

25) The Mechoulam actual example is not aerosolizable.

26) The Olsen reference confirmed the difficulties of formulating THC known by one of ordinary skill in the art.[24]

27) The Olsen reference teaches an inhalation aerosol of THC in 3 ml alcohol, 0.068 g Arlacel surfactant and 7.5 g CFC propellant.[25]

28) The Olsen reference states "Formulations of THC are difficult to prepare because of water insolubility and also because of the tacky nature of the pure material at room temperature. Early experiments demonstrated

[21]Peart Declaration, paragraph 17. See also Applicants' specification at page 9, line 11 (that THC is known to deteriorate during storage); id., paragraph bridging pages 10-11.

[22]See also Applicants' specification at page 9, lines 12-13.

[23]Weers Declaration executed March 27, 2006, paragraph 9 bridging pages 8-9.

[24]Peart Declaration, paragraph 13.

[25]Peart Declaration, paragraph 13.

excellent solubility of THC in conventional ethanol-difluorodichloromethane [propellant 12] - tetrafluorodichloro-ethane [propellant 114] solvent systems. Attempts at evaluation of these dosage forms in animals, however, indicated excessive tack of the spray and hence poor transport to the lungs."

29) The initial promise of a THC aerosol according to Olsen et al. (1975) never materialized, and in the past few decades, before Applicants' invention, it was conventionally thought that THC was not suited for aerosol-dispensing.[26]

30) One of ordinary skill in formulating THC would be aware of the long-standing lack of success in developing a THC aerosol.[27]

31) The actual experimentation of which a person of ordinary skill in the art at the time of Applicants' invention would have been given much greater weight than, and would have over-ridden, the generalized casual sentences in Mechoulam and Volicer which were unattached to any actual aerosol experimentation.[28]

32) Disadvantages of the oral form of THC (MARINOL) were known.[29]

33) Relative advantages of form of THC as inhaled marijuana smoke compared to the oral form of THC were known.[30]

34) Disadvantages of inhaled marijuana smoke were known, including medical factors and illegality in most jurisdictions.[31]

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[26] Applicants' specification, sentence bridging pages 10-11.

[27] Peart Declaration, paragraph 13.

[28] Peart Declaration, paragraph 13.

[29] Applicants' specification, paragraph bridging pages 6-7.

[30] Applicants' specification, paragraph bridging pages 7-8.

[31] Applicants' specification, paragraph bridging pages 7-8.

It is respectfully submitted to be in error for the Examiner to avoid reaching these many factual issues and to avoid making each of these factual findings, and to instead permit to stand impermissible hindsight reconstructions at odds with how a person of ordinary skill in the art at the time of Applicants' invention actually would have thought. When factual findings are made as requested above, it will be clear that the obviousness rejections are not supportable and run counter to how a person of ordinary skill in the art would reason and think.

C. Erroneous Assumptions Underlying the Obviousness Rejections

1) At page 5 of the Final Rejection, the Examiner's reading of Volicer column 5, lines 3-8, is at odds with how a person of ordinary skill in the art thinks, reasons and reads Volicer.

2) Also, the Examiner's statement at page 5 of the Final Rejection that "It is well within the capability of an ordinary skill artisan to adjust the amount of ethanol in an HFA formulation to obtain a solution" is not reasonable to apply to THC because persons of ordinary skill in the art were never previously formulating THC in HFA. Rather, it was Applicants who invented formulating THC in HFA and solved the previously insurmountable problems of non-CFC formulation of THC aerosols.

3) Moreover, the Examiner's statement at page 7 of the Final Rejection that an ordinary skill artisan would view Pars as teaching that THC compounds "are soluble in aqueous ethanolic formulations" and would then "have a reasonable expectation that these THC ester derivatives and salts thereof are soluble in HFA formulations comprising ethanol, due to the presence of ethanol in amounts up to 20% w/w" runs counter to how a person of ordinary skill in the art would think, as outlined in Dr. Peart's 1.132 Declaration (at paragraph 23) which explains in technical detail why "HFA would appear particularly unattractive and unhelpful for drugs already known to require high doses (such as THC which was thought to have a **significantly higher dosage** requirement than butixocort)." Moreover, the Examiner is assuming a too-simplistic approach to HFA formulation which is counter to the complexities of HFA

formulation which would be known to a person of ordinary skill in the art. "A person of ordinary skill in the art also would have had background experience and knowledge about the complexity of HFA formulation." (Dr. Peart's Declaration, paragraph 24.)

The above-mentioned assumptions and theories on which the Final Rejection are based are contrary to the thinking of a person of ordinary skill in the art and are therefore erroneous.

D. The Obviousness Rejection of Aerosol-Dispensable Composition Claims 57, 63 and Aerosolized Composition Claim 59 Over Mechoulam or Volicer in view of McNally; and the Obviousness Rejection of the Composition Claims Over Pars in view of McNally

Claim 57 recites an <u>aerosol-dispensable</u> pharmaceutical composition comprising THC and HFA, wherein the composition is <u>aerosol-dispensable</u>. Claim 63 recites a non-CFC <u>aerosol dispensable</u> pharmaceutical composition comprising THC.

The two primary references Mechoulam and Volicer contain examples, but no example which is aerosol-dispensable. The Examiner seems to readily admit (final office action, paragraph bridging pages 4-5) that Mechoulam's example, which is an oral non-inhalation administered peanut oil/THC composition, does not represent the closest prior art, yet the Examiner refuses to make of record an actual example in which there is an aerosol-dispensable THC composition. The Examiner persists in trying to elevate a speculative general statement in Mechoulam to the status of an actual example. The Examiner has given insufficient weight to the fact that Mechoulam completely lacks any THC-aerosol example, either prophetic or actual. The Examiner has given insufficient weight to the fact that there also is no THC-aerosol example, whether prophetic or actual, in Volicer.

A person of ordinary skill in the art, if he or she wanted to try to follow-up Mechoulam's general statement about a possible aerosol, seeing that Mechoulam (or Volicer) lacked any actual example of a THC aerosol, would look to the existing literature of THC aerosols; it would be completely illogical for the person of ordinary skill in the art to bother with a non-THC reference (McNally) to try to invent a THC

aerosol from scratch.

The Examiner's theory that a person of ordinary skill in the art would modify Mechoulam or Volicer in the direction of making an aerosol-dispensable pharmaceutical composition comprising THC that is novel and unlike the existing THC-aerosols is untenable.

Moreover, regarding Claim 57, the Examiner has made of record no evidence of THC and HFA having ever been formulated by anyone into any kind of composition before Applicants' discovery. The Examiner has given insufficient weight to the fact that there is no evidence of THC and HFA having been formulated together before Applicants' invention.

Nor has the Examiner made of record a single non-CFC aerosol-dispensable THC composition (as recited in Claim 63). The Examiner has given insufficient weight to the fact that there is no evidence that anyone before Applicants formulated a non-CFC THC aerosol.

The Examiner has given insufficient weight to the ample, uncontradicted evidence that the only aerosol-dispensable THC compositions within the grasp of a person of ordinary skill in the art to formulate would have been certain <u>CFC-containing</u> THC-aerosols. Moreover the Examiner has given insufficient weight to the uncontradicted evidence of record of the serious and unsolved difficulties of aerosolizing THC.

The reasons discussed above regarding Claims 57 and 63 likewise apply to Claim 59. Claim 59 recites an aerosolized pharmaceutical composition comprising respirable droplets comprising a THC.

In a second obviousness rejection, the Examiner cites Pars as the primary reference. Pars is no closer than Mechoulam or Volicer. None of the Pars examples are aerosols. For the same reasons discussed above with regard to the first obviousness rejection, the second obviousness rejection also cannot be maintained.

Moreover, it is clear that representative embodiments of Applicants' composition Claims 57, 59 and 63 provide pharmaceutically useful THC aerosols, and

that a representative embodiment of Mechoulam fails to do so. The actual example of Mechoulam is the representative embodiment. The Examiner cannot and does not deny that Mechoulam's actual example is non-aerosolizable. This must be accepted as evidence under MPEP 716.02 of the unexpected superiority of the presently claimed invention. The part of Mechoulam on which the Examiner proposes to rely, a non-example, is not a representative embodiment and the Examiner cannot purport to require Applicants to compare their claimed invention against something which does not exist in the prior art. The "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." MPEP 716.02(e), *citing In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987) and *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) for the rule that "Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 'would be requiring comparison of the results of the invention with the results of the invention.'" 357 F.2d at 422, 148 USPQ at 714.

The *prima facie* case of obviousness has been rebutted by Applicants. It is respectfully submitted that the obviousness rejections cannot be maintained.

ARGUMENT VIIE. REJECTION OTHER THAN 35 U.S.C. §§102, 103 AND 112

There is a non-statutory double patenting rejection which is not addressed in this appeal.

VIII. CLAIMS APPENDIX

The text of the claims involved in this Appeal are:

43. The aerosol-dispensable pharmaceutical composition of claim 57, comprising Δ^9-tetrahydrocannabinol, and up to 15 percent by weight of an organic solvent, said Δ^9-tetrahydrocannabinol and said organic solvent being dissolved in said hydrofluoroalkane to form a stable composition, wherein said Δ^9-tetrahydrocannabinol is present in said composition in concentrations ranging from 0.147% w/w (±0.008) to 5.940% w/w (±0.191).

46. The aerosol-dispensable pharmaceutical composition of claim 43 wherein said organic solvent comprises ethanol.

47. The aerosol-dispensable pharmaceutical composition of claim 43 wherein said solution consists essentially of said hydrofluoroalkane and said Δ^9-tetrahydrocannabinol.

48. The aerosol-dispensable pharmaceutical composition of claim 43 wherein said stable composition is surfactant free.

50. The aerosol-dispensable pharmaceutical composition of claim 57, comprising up to 15 percent by weight of an organic solvent, said tetrahydrocannabinol and said organic solvent being dissolved in said hydrofluoroalkane to form a stable composition, wherein said tetrahydrocannabinol is present in said composition in concentrations ranging from 0.147% w/w (±0.008) to 5.940% w/w (±0.191).

52. The aerosol-dispensable pharmaceutical composition of claim 50 wherein said tetrahydrocannabinol is a pharmaceutically acceptable salt of said

tetrahydrocannabinol.

53. The aerosol-dispensable pharmaceutical composition of claim 50 wherein said organic solvent comprises ethanol.

54. The aerosol-dispensable pharmaceutical composition of claim 50 wherein said solution consists essentially of said hydrofluoroalkane and said tetrahydrocannabinol.

55. The aerosol-dispensable pharmaceutical composition of claim 50 wherein said stable composition is surfactant free.

57. An aerosol-dispensable pharmaceutical composition comprising: tetrahydrocannabinol and hydrofluoroalkane, wherein the composition is aerosol-dispensable.

58. The aerosol-dispensable pharmaceutical composition of claim 57, comprising up to 15 percent by weight of an organic solvent, said tetrahydrocannabinol and said organic solvent being dissolved in said hydrofluoroalkane to form a stable composition.

59. An aerosolized pharmaceutical composition comprising: respirable droplets comprising a tetrahydrocannabinol.

60. The aerosolized pharmaceutical composition of claim 59, comprising a hydrofluoroalkane.

61. A method of aerosolizing a tetrahydrocannabinol, comprising:

dissolving a tetrahydrocannabinol in a hydrofluoroalkane and forming a stable pharmaceutical composition;

aerosolizing the stable pharmaceutical composition into respirable droplets comprising the tetrahydrocannabinol.

62. The method of claim 61, wherein the tetrahydrocannabinol is Δ^9-tetrahydrocannabinol.

63. A non-CFC aerosol-dispensable pharmaceutical composition comprising tetrahydrocannabinol (THC).

IX. Evidence Appendix

Evidence was submitted in this case under 37 C.F.R. 1.130, 1.131, or 1.132, namely:

Declaration of Joanne Peart Under 37 C.F.R. 1.132 executed November 6, 2007 (filed November 7, 2007), a copy of which is submitted herewith;

"Material Safety Data Sheet for Peanut Oil," attached to Dr. Peart's Declaration, and a copy of which is submitted herewith;

Orla et al., "Nebulizatin of Fluids of Different Physicochemical Properties with Air-Jet and Ultrasonic Nebulizers" (1995), attached to Dr. Peart's Declaration, and a copy of which is submitted herewith;

Davis, "Physico-chemical Studies on Aerosol Solutions for Drug Delivery I. Water–Propylene Glycol Systems" (1977), attached to Dr. Peart's Declaration, and a copy of which is submitted herewith;

Declaration of Jeffrey G. Weers Under 37 C.F.R. 1.132, executed March 27, 2006 (filed April 3, 2006), a copy of which is submitted herewith.

X. RELATED PROCEEDINGS APPENDIX

There are none.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

Peart et al.

Serial No. 10/759,280

Filed: January 20, 2004

Confirmation No. 6861

Group Art Unit: 1616

Examiner: Alstrum Acevedo, James Henry

For: "Δ^9 *TETRAHYDROCANNABINOL* (Δ^9 *THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE*"

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOANNE PEART UNDER 37 C.F.R. 1.132

Dear Sir:

1. I am currently employed by Virginia Commonwealth University ("VCU") which owns the above-identified patent application.

2. I hold the position of Associate Professor, Department of Pharmaceutics, in the School of Pharmacy, which position I have held since July 2006. Previously, from January 1998 to June 2006, I held the position of Assistant Professor, in VCU's Department of Pharmaceutics. Previously, from February 1996 to December 1997, I was Visiting Assistant Professor in VCU's Department of Pharmaceutics.

3. I am an inventor of the above-identified patent application, and of United States Patent Nos. 6,509,005 and 6,713,048.

4. In my work for VCU, my focus is: aerosol electrostatics, aerosolization; formulation, regional lung deposition and in vitro testing aspects of powder aerosols and metered dose inhalers (MDIs); and the role of packaging components on aerosol electrostatics.

5. My education includes a Bachelor's Degree in Pharmacy from University of Bath

(1991) and a Ph.D. in Pharmaceutical Sciences from the University of Bath (1996). I am a registered Pharmacist in Great Britain (Member of the Royal Pharmaceutical Society of Great Britain, 1992).

6. Some books, book chapters and other publications of which I am a co-author or co-editor include but are not limited to:

Dalby RN, Byron PR, Peart, J and Suman JD, Editors, RDD Europe 2007, Davis Healthcare International Publishing, IL, 2007.

Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, editors: Respiratory Drug Delivery 2006, Volumes I, II and III, Davis-Healthcare International, River Grove, IL.

Keil J, Kotian R and Peart J: "Using and interpreting aerosol electrostatic data using the electrical low pressure impactor (ELPI)," Respiratory Drug Delivery 2006: 267-278, 2006.

Peart J, Kulphaisal P, and Orban, JC: "Relevance of Electrostatics in Respiratory Drug Delivery," PharmaGenerics; 84-87, 2003.

Wilson DM, Peart, J, Martin BR, Bridgen TR, Byron PR and Lichtman, AH. "Physicochemical and Pharmacological Characterization of a Delta-9-Tetrahydrocannabinol aerosol generated by a Metered Dose Inhaler." Drug and Alcohol Dependence, (3) 259-267, 2002.

Peart J, Orban JC, McGlynn P, Redmon MP, Sargeant CM and Byron PR: "MDI electrostatics: Valve and formulation interactions that really make a difference," Proceedings of Respiratory Drug Delivery VIII, Davis Horwood International: Raleigh, NC, pp. 223-230, 2002.

Clarke, MJ, Peart J, Cagnani, S and Byron PR, "Adhesion of powders for inhalation: an evaluation of drug detachment from surfaces following deposition from aerosol streams." Pharmaceutical Research, 19, 322-329, 2002.

7. I have reviewed the pending claims in the above-identified patent application, the office action dated June 15, 2007 which has been entered in this application, and the references relied upon by the Examiner for the obviousness rejections.

8. At page 3 of the June 15, 2007 office action, an obviousness rejection has been made of claims 43, 46-48, 50, 53-55, 57-60 based on either Mechoulam et al or Volicer et al as the primary reference, in view of McNally et al. At page 4 of the office action, claim 52 is said to be

rejected for obviousness based on the mentioned combination of references plus Pars.

9. Mechoulam et al (USP 5,539,993) includes Pharmacological Examples beginning at column 9. In all of the actual examples, Mechoulam et al were using **peanut oil**, administered **orally** to mice. (Column 10, footnote 2 to Table I, footnote 5 to Table II, lines 62-63; column 11, footnote 8 to Table III; column 12, footnote 14 to Table V). Mechoulam et al lacks any data or information from which a person of ordinary skill in the art could formulate and administer THC via inhalation in a pharmaceutically acceptable way. Mechoulam et al's actual examples in which peanut oil are used for oral administration would not and cannot be extrapolated by such a person of ordinary skill in the art to a pharmaceutical aerosol.

10. Peanut oil is an unacceptable vehicle to produce a pharmaceutical aerosol for the following reasons: Peanut oil is a nonvolatile, colorless to pale yellow highly viscous liquid. The viscosity for peanut oil is 39.6 mm^2/s (see attached 'Oil Types and Filtering', www.vegburner.co.uk) with a reported vapor pressure of 0 mmHg at 20°C. (*See* attached Material Safety Data Sheet for Peanut Oil, Mallinckrodt Baker, Phillipsburg, NJ). Also, peanut oil also carries the warning report that it "may cause irritation to the respiratory tract. Symptoms may include coughing and shortness of breath". (*Id.*) Peanut oil is unuseable as a vehicle in an MDI because peanut oil does not have an appropriate vapor pressure. The vehicle in an MDI must provide the energy to produce a fine aerosol spray of drug particles for pulmonary deposition. Vapor pressure is defined as the pressure of a vapor in equilibrium with its non-vapor phases. Liquified gas propellants were preferred for the vehicle in MDIs because they maintain a constant vapor pressure at a constant ambient pressure during normal usage and emptying of the pack. The vapor pressure of a MDI system is typically in the range 50-100 psia (Metered Dose Inhaler Technology, Purewal and Grant, 1998). One of ordinary skill in the art at the time the claimed invention of the above-referenced application was made would not have been motivated to use peanut oil as a vehicle in an MDI as he or she would realize that Mechoulam's teaching that THC derivatives are soluble in peanut oil does not solve the problem, of which he or she would know, of peanut oil lacking appropriate vapor pressure to produce an MDI.

11. Furthermore, I have conducted experimentation in which I packaged peanut oil in an

MDI canister and observed that the peanut oil **failed** to produce an aerosol spray, let alone produce a spray capable of producing respirable droplets. This failure of the peanut oil is as expected by a person of ordinary skill in the art, and is evidence that he or she would have failed had he or she tried to work along the lines hypothesized in the office action. Namely, I prepared an MDI with peanut oil and observed that, as I had expected and as a person of ordinary skill in the art at the time of my invention would have expected, nothing comes out of the MDI when peanut oil is used as the vehicle. This observation that peanut oil does not dispense from an MDI is consistent with peanut oil's lack of vapor pressure.

12. Nor would peanut oil be thought by a person of ordinary skill in the art to have been useable in a dry powder inhaler or a nebuliser, which are other types of aerosol delivery devices. It would be apparent to one of ordinary skill in the art that peanut oil would not be a suitable vehicle for dry powder inhalers or nebulisers. Peanut oil is a highly viscous liquid (viscosity = 39.6 mm^2/s which approximates to 39.6 centiPoise (cP), assuming density = $1 g/cm^3$) and would be unsuitable as a vehicle for a nebuliser solution. Nebuliser solutions are typically aqueous based systems and THC-like derivatives were known to be very poorly water soluble. The effects of viscosity on nebulization efficiency using both air jet and ultrasonic nebulizers has been studied (Nebulization of Fluids of Different Physicochemical Properties with Air Jet and Ultrasonic Nebulizers, Orla N M McCallion, Kevin M G Taylor, Marian Thomas and Anthony J Taylor, Pharmaceutical Research Vol. 12, 1682-1688, 1995, which article is attached hereto). Table 1 from this article summarizes the Mean Mass Median Diameter and Total Output of a range of fluids nebulised in an air jet nebulizer. Aqueous based systems have a viscosity of approximately 1cP. As the viscosity increases, the MMD decreases but the output also decreases. This has been reported previously (Physicochemical Studies on Aerosol Solutions for Drug Delivery I. Water - Propylene Glycol Systems, S.S. Davis, International Journal of Pharmaceutics, 1, 71-83, 1978, a copy of which is attached hereto.) The authors concluded that the more viscous fluids required longer nebulization times, and were associated with increased residual amounts (lower outputs). While the fluids of high viscosity produced aerosols with smaller MMDs in jet nebulizers, they were considered to be unsuitable for clinical application due to poor patient compliance (long nebulization times) and low efficiency. Table 2 from this

article summarizes the Mean Mass Median Diameter and Total Output of a range of fluids nebulized in an ultrasonic nebulizer and indicates that these nebulizers were unable to nebulize the more viscous fluids (viscosity > 5 cP). In summary, the use of peanut oil as a vehicle in a nebulizer formulation would not be appropriate, and such use would have been rejected by a person of ordinary skill in the art.

13. Moreover, a person of ordinary skill in the art would have considered how little success THC aerosols had then shown as discussed in Ohlsen, Hartley et al., and Tashkin et al. Ohlsen confirmed the difficulties of formulating THC known by one of ordinary skill in the art. Ohlsen et al teaches an inhalation aerosol of THC comprised of THC in 3 ml alcohol, 0.068 g Arlacel surfactant and 7.5 g CFC propellant. The reference states "Formulations of THC are difficult to prepare because of water insolubility and also because of the tacky [sticky] nature of the pure material at room temperature. Early experiments demonstrated excellent solubility of THC in conventional ethanol-difluorodicholoromethane [propellant 12]-tetrafluorodichloroethane [propellant 114] solvent systems. Attempts at evaluation of these dosage forms in animals, however, indicated excessive tack of the spray and hence poor transport to the lungs." One of ordinary skill in the art would have recognized that the majority of the dose metered by this formulation which contained 23% ethanol, would result in very high deposition of drug in the patient's throat [because the droplet size emitted by the preparation is largely non-respirable, due to the high concentration of low volatility ethanol and surfactant]. One of ordinary skill in formulating THC would be aware of the long-standing lack of success in developing a THC aerosol. Such actual experimentation of which a person of ordinary skill in the art at the time of my and my colleagues' invention would have been aware would have been much given greater weight than, and would have over-ridden, the generalized casual sentences in Mechoulam and Volicer which were unattached to any actual aerosol experimentation.

14. The McNally reference cited in the office action fails to disclose any actual THC example and is for a completely different drug, butixocort, which is unlike THC. THC and butixocort (or, for that matter, almost any other drug) definitely are **not** thought of as interchangeable for purposes of an aerosol formulation. The properties of THC are dissimilar from drugs that generally may be formulated into aerosols. The difficulty of working with THC,

large dosage amounts required for systemic administration of THC, and properties of THC that make it unlike, and not interchangeable with, most other drugs were well documented in the literature. For example, as stated in Dewey, W.L., Cannabinoid Pharmacology, Pharmacological Reviews, 38: 151-172 (1986), THC resembles rubber-cement, rather than a powder like most drugs, and thus present formulation difficulties. A person of ordinary skill in the art would have been aware of the challenges of working with THC. One known significant problem in working with THC is that it is very lipid soluble and hydrophobic, difficult to handle, and a gummy-type material like "rubber cement." See, e.g., Dewey, *supra*. A further known difficulty in working with THC has been the inability of grinding THC (a resinous material) into a microfine powder.

15. In MDIs, generally speaking, the drug substance is either suspended or dissolved in the propellant mixture which usually contains a surface active agent. Partial dissolution is undesirable because partial dissolution leads to crystal growth, resulting in deterioration of product performance. For the formulations that contain the drug substance suspended in propellant the drug is usually ground to a microfine powder before incorporation into the propellant mixture.

16. THC as a resinous material cannot be ground into a microfine powder.

17. The person of ordinary skill in the art, further knowing the challenges of making MDIs (see, e.g., Byron, P.R., Aerosol formulation, generation and delivery using metered systems, in: Byron, PR (Ed.), Respiratory Drug Delivery (CRC Press, Boca Raton, FL, 1990), pp. 167-204 (especially see pages 187-201, detailing strategies which must be followed during MDI formulation); Purewal, T.S., Formulation of Metered Dose Inhalers, in: Purewal, T.S. and Grant, D.J.W., Metered Dose Inhaler Technology (Interpharm Press, 1997), pp. 9-68) thus would **not** view THC as sufficiently soluble or stable to be used in a formulation to achieve necessary metered and respirable doses.

18. Because of these above-mentioned scientific and technical facts and background, a person of ordinary skill in the art reading about McNally's butixocort aerosol formulation would **not** think in terms of substituting THC for butixocort.

19. Also, it should be appreciated that the structures of Butixocort Propionate and THC are very different and it is inappropriate to compare them. In the office action dated January 9,

2007, on page 7, the structures of Butixocort Propionate and Tetrahydrocannabinol have been shown – clearly two very disparate structures.

20. Nor does THC share the property of Butixocort Propionate (a corticosteroid) of being administrable in low doses. (Typical doses to the lung for corticosteroids range from 20-50μg.) To the contrary, THC (which is not a corticosteroid) requires high dose administration. Oral doses from Marinol (THC) indicate 2.5 - 10 mg are needed; assuming 10% bioavailability, that translates to 0.25-1mg (250-1000μg). Therefore ten times as much THC needs to be administered to the lungs compared to corticosteroids because systemic, not local, action is at work.

21. Because Butixocort Propionate can be administered in low doses, its poor solubility (e.g., the solubility of butixocort propionate in HFA 134 is about 0.02% by weight and in HFA 227 is about 0.03% by weight; *see* McNally, column 1, lines 44-47) is tolerable.

22. The solubility of a range of compounds (such as albuterol base, albuterol sulfate, beclomethasone dipropionate, oleic acid, sorbitan trioleate, etc.) is low in HFA 134a. The solubility in HFA134a of albuterol base and albuterol sulfate is <0.0005% w/w (Tzou et al. 1997); of beclomethasone dipropionate is 0.03% w/w (Vervaet & Byron, 1999); of oleic acid is <0.02% w/w (Vervaet & Byron, 1999); of sorbitan trioleate is <0.02% w/w (Vervaet & Byron, 1999).

23. With such data in mind about low solubility in HFA for a range of drugs, HFA would appear particularly unattractive and unhelpful for drugs already known to require high doses (such as THC which was thought to have a **significantly higher dosage** requirement than butixocort).

24. A person of ordinary skill in the art also would have had background experience and knowledge about the complexity of HFA formulation. See, e.g., Tansey, I.P., Changing to CFC Free Inhalers: The technical and clinical challenges, *Pharm J*, 250:896-898 (1997); Vervaet, C., Byron, P.R., Drug-surfactant-propellant interactions in HFA formulations, *Internat'l J of Pharmaceutics*, 86:13-30 (1999).

25. A person of ordinary skill in the art knew that the propellant must be appropriate for the application, and that a particular propellant used with one drug is not necessarily appropriate (nor assumed to be appropriate) for use with any other drug. A person of ordinary skill in the art

would have been thinking in terms of solubility, particle size, delivered dose needed, etc. of the drug, and further would be thinking of chemical properties of a particular propellant. Such considerations would be foremost in the mind of a person of ordinary skill in the art, and as discussed above the obviousness rejections in the office action are based on assumptions inconsistent with such considerations of which a person of ordinary skill would have been thinking.

26. The Mechoulam et al actual formulation examples are all for administering THC **orally** in peanut oil to mice. Pharmacokinetics of THC given orally provide an onset of pharmacological action in a range of about 30 to 180 minutes with peak plasma levels in a range of about 60 to 480 minutes (*see* Table 2 in the Background section of the specification). By contrast, a representative embodiment of Claim 57 of the above-identified application is an aerosol-dispensable pharmaceutical composition comprising: THC and HFA, wherein the composition is **aerosol-dispensable**; a representative embodiment of Claim 59 of the above-identified application is an aerosolized pharmaceutical composition comprising **respirable droplets** comprising a THC. Such inventive aerosol-dispensable compositions and aerosolized pharmaceutical compositions actually have been made and tested by me and under my direction. *See, e.g.*, Tables 4A, 4B at pages 16-17 of the specification. In Mechoulam et al., the drugs were administered orally **90 minutes** before the hot plate test. (*See* column 11, line 42.) By contrast, in representative embodiments of the invention, effective levels of THC are achieved **20 minutes** (and sooner) after inhalation treatment. *See* Table 6 at page 26 of the specification.

27. Our presently claimed invention achieves "superior" results over Mechoulam et al with regard to rapidity of THC reaching blood and brain.

28. The invention does so without resorting to injection mode or banned CFC mode or "non-medical" mode (i.e. smoking).

29. Aside from use of banned CFC, use of injection, or use of "non-medical" (smoking), and putting aside our presently claimed invention, persons in the art at the time of our invention knew of no faster way to deliver THC to blood and brain than Mechoulam et al's oral dosage actual example.

30. It was unexpected that THC actually could be successfully aerosolized in a non-CFC

formulation. *See also* the paragraph bridging pages 10-11 of the specification.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Joanne Peart

November 6 2007.

Date

MSDS Material Safety Data Sheet

24 Hour Emergency Telephone: 908-859-2151
CHEMTREC: 1-800-424-9300
National Response in Canada
CANUTEC: 613-996-6666
Outside U.S. And Canada
Chemtrec: 703-527-3887

From: Mallinckrodt Baker, Inc.
222 Red School Lane
Phillipsburg, NJ 08865

J.T.Baker

NOTE: CHEMTREC, CANUTEC and National Response Center emergency numbers to be used only in the event of chemical emergencies involving a spill, leak, fire, exposure or accident involving chemicals.

All non-emergency questions should be directed to Customer Service (1-800-582-2537) for assistance.

Peanut Oil

1. Product Identification

Synonyms: Oils, peanut, Groundnut oil
CAS No.: 8002-03-7
Molecular Weight: Not applicable to mixtures.
Chemical Formula: N/A
Product Codes: S901

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent	Hazardous
Peanut Oil	8002-03-7	98 - 100%	Yes

3. Hazards Identification

Emergency Overview

WARNING! CAUSES IRRITATION TO SKIN, EYES AND RESPIRATORY TRACT.

SAF-T-DATA(tm) Ratings (Provided here for your convenience)

Health Rating: 1 - Slight
Flammability Rating: 1 - Slight
Reactivity Rating: 1 - Slight
Contact Rating: 2 - Moderate
Lab Protective Equip: GOGGLES; LAB COAT; PROPER GLOVES
Storage Color Code: Green (General Storage)

Potential Health Effects

Inhalation:
May cause irritation to the respiratory tract. Symptoms may include coughing and shortness of breath.
Ingestion:
Large oral doses may cause irritation to the gastrointestinal tract.
Skin Contact:
May cause irritation with redness and pain.
Eye Contact:
May cause irritation, redness and pain.
Chronic Exposure:
No information found.
Aggravation of Pre-existing Conditions:
No information found.

4. First Aid Measures

Inhalation:
Remove to fresh air. Get medical attention for any breathing difficulty.
Ingestion:
If large amounts were swallowed, give water to drink and get medical advice.
Skin Contact:
Immediately flush skin with plenty of water for at least 15 minutes. Remove contaminated clothing and shoes. Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention if irritation develops.
Eye Contact:

Immediately flush eyes with plenty of water for at least 15 minutes, lifting upper and lower eyelids occasionally. Get medical attention if irritation persists.

5. Fire Fighting Measures

Fire:
Flash point: 282C (540F) OC
Autoignition temperature: 443C (829F)
Slight fire hazard when exposed to heat or flame.
Explosion:
Above the flash point, explosive vapor-air mixtures may be formed.
Fire Extinguishing Media:
Water, dry chemical, foam or carbon dioxide.
Special Information:
In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

6. Accidental Release Measures

Ventilate area of leak or spill. Remove all sources of ignition. Wear appropriate personal protective equipment as specified in Section 8. Isolate hazard area. Keep unnecessary and unprotected personnel from entering. Contain and recover liquid when possible. Use non-sparking tools and equipment. Collect liquid in an appropriate container or absorb with an inert material (e. g., vermiculite, dry sand, earth), and place in a chemical waste container. Do not use combustible materials, such as saw dust. Do not flush to sewer!

7. Handling and Storage

Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Keep from contact with oxidizing materials. Containers of this material may be hazardous when empty since they retain product residues (vapors, liquid); observe all warnings and precautions listed for the product.

8. Exposure Controls/Personal Protection

Airborne Exposure Limits:
None established.
Ventilation System:
In general, dilution ventilation is a satisfactory health hazard control for this substance. However, if conditions of use create discomfort to the worker, a local exhaust system should be considered.
Personal Respirators (NIOSH Approved):
If the exposure limit is exceeded and engineering controls are not feasible, a half facepiece particulate respirator (NIOSH type P95 or R95 filters) may be worn for up to ten times the exposure limit or the maximum use concentration specified by the appropriate regulatory agency or respirator supplier, whichever is lowest.. A full-face piece particulate respirator (NIOSH type P100 or R100 filters) may be worn up to 50 times the exposure limit, or the maximum use concentration specified by the appropriate regulatory agency, or respirator supplier, whichever is lowest. Please note that N filters are not recommended for this material. For emergencies or instances where the exposure levels are not known, use a full-facepiece positive-pressure, air-supplied respirator. WARNING: Air-purifying respirators do not protect workers in oxygen-deficient atmospheres.
Skin Protection:
None required.
Eye Protection:
Use chemical safety goggles and/or a full face shield where splashing is possible. Maintain eye wash fountain and quick-drench facilities in work area.

9. Physical and Chemical Properties

Appearance:
Colorless to pale yellow liquid.
Odor:
Faint pleasant odor.
Solubility:
Negligible (< 0.1%)
Specific Gravity:
0.91
pH:
No information found.
% Volatiles by volume @ 21C (70F):
0
Boiling Point:
No information found.
Melting Point:
Solidifies at about -5C. Clouds at low room temperature.
Vapor Density (Air=1):
No information found.
Vapor Pressure (mm Hg):
0 @ 20C (68F)
Evaporation Rate (BuAc=1):
No information found.

10. Stability and Reactivity

Stability:
Stable under ordinary conditions of use and storage. Very slowly thickens and becomes rancid on prolonged exposure to air.
Hazardous Decomposition Products:
Carbon dioxide, carbon monoxide
Hazardous Polymerization:
Will not occur
Incompatibilities:
Strong oxidizing agents.
Conditions to Avoid:
No information found

11. Toxicological Information

Peanut oil: human skin: 300 mg/3D intermittent, mild. Rabbit skin: 100 mg/24H moderate. Investigated as a tumorigen, mutagen.

--------\Cancer Lists\--------

Ingredient	---NTP Carcinogen--- Known	Anticipated	IARC Category
Peanut Oil (8002-03-7)	No	No	None

12. Ecological Information

Environmental Fate:
No information found.
Environmental Toxicity:
No information found.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Not regulated

15. Regulatory Information

--------\Chemical Inventory Status - Part 1\--------

Ingredient	TSCA	EC	Japan	Australia
Peanut Oil (8002-03-7)	Yes	Yes	No	Yes

--------\Chemical Inventory Status - Part 2\--------

Ingredient	Korea	--Canada-- DSL	NDSL	Phil.
Peanut Oil (8002-03-7)	Yes	Yes	No	Yes

--------\Federal, State & International Regulations - Part 1\--------

Ingredient	-SARA 302- RQ	TPQ	------SARA 313------ List	Chemical Catg.
Peanut Oil (8002-03-7)	No	No	No	No

--------\Federal, State & International Regulations - Part 2\--------

Ingredient	CERCLA	-RCRA- 261.33	-TSCA- 8(d)
Peanut Oil (8002-03-7)	No	No	No

Chemical Weapons Convention: No TSCA 12(b): No CDTA: No
SARA 311/312: Acute: Yes Chronic: No Fire: No Pressure: No
Reactivity: No (Pure / Liquid)

Australian Hazchem Code: None allocated
Poison Schedule: None allocated
WHMIS:
This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

16. Other Information

NFPA Ratings: Health: 1 Flammability: 0 Reactivity: 0
Label Hazard Warning:
WARNING! CAUSES IRRITATION TO SKIN, EYES AND RESPIRATORY TRACT.
Label Precautions:
Avoid contact with eyes, skin and clothing.
Wash thoroughly after handling.
Avoid breathing dust.
Keep container closed.
Use with adequate ventilation.
Label First Aid:
If inhaled, remove to fresh air. Get medical attention for any breathing difficulty. In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes.
Product Use:
Laboratory Reagent.
Revision Information:
MSDS Section(s) changed since last revision of document include: 3.
Disclaimer:

Prepared by: Environmental Health & Safety
Phone Number: (314) 654-1600 (U.S.A.)

Nebulization of Fluids of Different Physicochemical Properties with Air-Jet and Ultrasonic Nebulizers

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Purpose. Empirical formulae relate the mean size of primary droplets from jet and ultrasonic nebulizers to a fluid's physicochemical properties. Although the size selective "filtering" effects of baffling and evaporation may modify the secondary aerosol produced, this research sought to evaluate whether viscosity and surface tension of nebulized fluids influenced the aerosol's size and output characteristics.

Methods. Fluid systems of different surface tension and viscosity (glycerol and propylene glycol solutions [10–50% (v/v)] and a range of silicone fluids [200/0.65 cs – 100cs]) were nebulized in three jet and two ultrasonic nebulizers. Secondary aerosol characteristics were measured with a Malvern 2600C laser diffraction sizer and the nebulization times, residual volumes and percentage outputs were determined.

Results. While the droplet size appeared to be inversely proportional to viscosity for jet nebulizers, it was directly proportional to viscosity for ultrasonic nebulizers. Although fluid systems with lower surface tensions generally produced slightly smaller MMDs, the relationship between surface tension and droplet size was complex. The more viscous fluids required longer nebulization times and were associated with increased residual amounts (lower outputs). The ultrasonic nebulizers did not effectively, and were on occasion unable to, nebulize the more viscous fluids.

Conclusions. It follows that there are cut-off values for viscosity and/or surface tension above or below which ultrasonic devices fail to operate. Moreover, jet nebulizers generated an aerosol with an optimum respirable output from median-viscosity fluids.

KEY WORDS: aerosol; droplet size; jet nebulizer; surface tension; ultrasonic nebulizer; viscosity.

INTRODUCTION

Early studies on airblast atomisation elucidated some of the key factors involved. While the range of variables covered was fairly narrow, it was suggested that droplet-size was inversely proportional to the relative velocity between the air and the liquid and proportional to the liquid's surface tension (for low viscosity liquids); and that viscosity had a decreasing effect on droplet-size as the air/liquid ratio increased. Rizkalla and Lefebvre (1) suggested that the mean drop-size of liquid sprays increased with increases in liquid viscosity and surface tension while the overall effect of liquid density on drop-size was small. Mercer (2) found similar results in his research with nebulizers, stating that the primary droplet distribution was related to:

$$D/D_L = 0.64[1 + 0.011(G_L/G_A)^2] \times [2\gamma/9\rho V^2 D_L]^{0.45}$$

where D = diameter of droplet of average volume, D_L = diameter of liquid inlet orifice, G_L, G_A = mass flow rate of liquid and air, γ = liquid surface tension, ρ = air density and V = air velocity.

Viscosity differences of the magnitude (1–20 cs) were reported to have a negligible effect on average droplet-size (3) and affected mean droplet volume only through the liquid mass flow rate (G_L). Liquid viscosity resists droplet formation at all stages, hence higher viscosities had been expected to increase the size of the droplet. Work by Searls and Snyder (3) revealed that increased viscosity prolonged atomisation time but reduced mean droplet-size. Dorman (4) reported that d_{32} (the volume surface or Sauter mean diameter) was proportional to $\eta^{0.1}$, while Hasson and Mizrahi (5) found that d_{32} was proportional to $\eta^{1/6}$ for values of viscosity from 1–21 cP. However, Hinds *et al.* (6) noted little change in drop-size with increased viscosity. Mercer's equation posits that reducing the surface tension should produce smaller droplets. However, there is insufficient consistent confirmatory research in this area. Walkenhorst and Dautrebande (7) stated that surface tension exerted no real effect on the resultant aerosol, whilst Kouchetov *et al.* (8) reported that, when solutions containing a surface active agent were atomised by high velocity air streams, the resultant droplet-size was similar to water's. However, further studies by Fainerman and Sapiro (9) revealed that surfactant solutions emitted smaller droplets than water.

There have been few previous attempts to assess how medical air-jet atomisers (nebulizers) perform when using solutions of differing physical properties. Maximyst and Bird jet nebulizers were used to nebulize a range of propylene glycol solutions [10% to 60% (v/v)]. Above 20%, MMDs and aerosol output decreased with increased propylene glycol content. Furthermore, as surface tension decreased, the aerosol output increased (10). Newman *et al.* (11) reported than Bird, DeVilbiss and Upmist jet nebulizers tended (though not significantly) to produce smaller droplets from higher-viscosity solutions. They could not, by contrast, demonstrate a clear correlation between droplet-size and the solutions' surface tensions. Medical ultrasonic nebulizers invariably belong to the high frequency (1–3 MHz) piezoelectric type. Two rival theories—the capillary and the cavitation theories—each purport to describe the mechanism of liquid disintegration in ultrasonic devices. The former depicts droplet formation as the result of capillary waves on the excited liquid surface growing in amplitude until the crests break off. Lang (12) observed that the mean drop-size from thin liquid layers was proportional to the capillary wavelength on the liquid surface. Using an experimentally determined factor of 0.34, the drop diameter D was given by the relationship:

$$D = 0.34 \times (8\pi\gamma)^{1/3}/\rho f^2$$

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App. 14

where γ = surface tensions; ρ = density and f = excitation frequency. However Sollner's (13) cavitation theory may explain how liquid disintegrates in high frequency nebulizers. This postulates that the liquid is atomised by hydraulic shocks produced by an implosion of cavitation bubbles near its surface. Later research (14,15) using relatively high frequencies (0.5–2.0 MHz) indicated that atomisation was a cavitation-dependent phenomena. Boguslavskii and Eknadiosyants (16) convincingly married these theories when they proposed that drop formation resulted from capillary waves initiated and driven by cavitation bubbles. Thus, if capillary theory contributes in part to ultrasonic atomisation, the droplet-size will be proportional to the surface tension of the liquid and inversely proportional to the liquid's density. Furthermore, variation in liquid properties giving increased threshold amplitude (e.g. increased viscosity) will tend to progressively slow or completely suppress the rate of atomisation.

Boucher and Kreuter (17) reported that solutions with viscosity above 10 cP were difficult to aerosolise with ultrasonic nebulizers. Gershenzon and Eknadiosyants (14) stated that liquid vapour pressure and viscosity were important factors in ultrasonic aerosol output in that liquids with a low viscosity offered less resistance to fountain-disintegration and produced greater "fog" outputs. The rate of ultrasonic nebulization of Alevaire (a drug for mucus clearance) progressively decreased as the viscosity of the drug solution increased (15). Similarly, the output rate of N-acetyl-L-cysteine was increased by 10% when a less viscous solution (10% as opposed to 20%) was nebulized. Furthermore, whilst certain oily/viscous liquids produced a fountain, they did not disintegrate and produced only fountain whirling and foaming with no aerosol generated (15). Variations in air/liquid surface tension may be less significant. Surfactants have been shown to depress nebulization rate, possibly due to a reduction in capillary wavelength causing an increase in the threshold amplitude (17), or to their influence on the diffusion of gas into cavitation bubbles (18).

There are insufficient studies of the effect of formulation variables upon the size and output characteristics of nebulized medical aerosols. This study sought to address this by investigating aerosol characteristics from a diverse range of fluids nebulized in three types of jet nebulizer and two ultrasonic devices.

MATERIALS AND METHODS

Fluids, selected to encompass a wide range of surface tension and viscosity, included deionised water (Whatman WR 50 RO/Deioniser, Whatman U.K.), ethanol, glycerol 10–50% (v/v) solutions, propylene glycol 10–50% (v/v) solutions (B.D.H. Laboratory Supplies, Lutterworth, U.K.) and silicone fluids 200/0.65 cs–200/100 cs (Dow Corning, Reading, U.K.). The surface tension of the fluids tested were determined using the CAHN Dynamic Contact Angle analyser (Scientific and Medical Products Ltd., Manchester, U.K.). The viscosities were determined using a U-tube viscometer and the bulk densities determined using standard density bottles (B.D.H. Laboratory Supplies, Lutterworth, U.K.). These fluids were nebulized to dryness or for (1) 20 min in three jet nebulizers [Pari LC (Pari-Werk GmbH, Starnberg, Germany), Sidestream (Medic Aid Ltd., Pagham, U.K.) and Cirrus (Intersurgical Complete Respiratory Care, Wokingham, U.K.)] driven by compressed air from a gas cylinder at 6 L/min and 8 L/min or (2) nebulized for 10 min in two ultrasonic nebulizers [Medix Electronic and Easimist (Medix Ltd., Lutterworth, Leicestershire)] operated at the mid-point power setting. The Malvern 2600C laser particle sizer (Malvern Instruments, Malvern, U.K.) was used to obtain a continual measurement of aerosol droplet size distribution throughout the entire nebulization period. Readings were taken at 30 sec intervals. Each nebulizer was weighed: (1) when empty, (2) following the addition of the appropriate volume of test fluid (4 to 8 ml) and (3) at the end of the nebulization period. The "dead volume" of the test fluid was calculated from the weight measurements. Optimal alignment of the equipment and background measurements were measured prior to nebulization. The nebulizer was clamped in a vertical position so that the mouth-piece tip was 2.5 cm from the centre of the laser beam. The aerosol was directed through the beam approximately 5 mm in front of the 63 mm Fourier transform lens and was drawn away by extraction into a suction pump. The nebulizers were run at the appropriate flow-rate for 10 sec before measurement in order to achieve a steady output. All experiments were performed in triplicate at ambient temperature (20–25°C) and relative humidity (40–60%). The various parameters relating to aerosol characteristics and nebulization process which were investigated included:

i. The mass median diameter (MMD). Assuming that the nebulized droplets are spherical, it is possible to calculate the aerodynamic diameter from the bulk density values (relative to water) and MMD values.

ii. The percentage of the aerosol droplets less than 5 μm in diameter (i.e. respirable percentage) and the 90% undersize.

iii. The span value. This is a measure of the width of the volume distribution relative to the median diameter.

$$\text{Span} = \frac{90\% \text{ undersize} - 10\% \text{ undersize}}{50\% \text{ undersize}}$$

iv. The time required to nebulize the test fluid to dryness (i.e. the time at which no aerosol could be detected with the sizing equipment) or to a predetermined maximum time.

v. The weight of the test fluid remaining in the device after nebulization. This permitted calculation of the percentage of the initial fluid which remained in the nebulizer and of the total output.

vi. The respirable output (respirable percentage multiplied by the total output percentage) for the appropriate nebulization period.

RESULTS AND DISCUSSION

While empirical formulae relate the mean size of the primary droplets produced by nebulizers to the viscosity, surface tension and density of the fluid, these effects may be masked in the secondary aerosol produced. The marked discrepancies noted in this and other studies between predicted and actual outcomes may be attributable to nebulizer design. Baffle systems are designed to trap more than 99% of the primary droplet mass. This is mostly returned to the reser-

voir, and less than 1% (comprising only the smallest satellite droplets) is emitted at the mouthpiece. The wall of the device may also act as a baffle in small-dimension nebulizers. Consequently, these size-selective "filtering" effects may mask any effects of viscosity and surface tension on the primary droplets produced at the point of atomisation. Furthermore, dependent on the sizing technique adopted, droplet-size may be modified by droplet evaporation (or hygroscopic growth). In this study, drop-sizes were measured by a laser diffraction sizer at a standardised distance of 2.5 cm from the atomiser mouth-piece, since this distance corresponds to the arrival of the aerosol at the patient's respiratory tract. This technique can measure droplets close to their point of generation (before appreciable evaporation or growth can occur) and is therefore an ideal method to characterise aerosols delivered from medical nebulizers. Clark (19) found this a "robust and reliable" technique which allowed him to validate a good correlation between diffraction derived size distribution, gamma camera deposition profiles and the theoretical Rudolph model.

Mass Median Diameter. This study's most prominent finding was the MMD's apparently greater dependence upon the nebulizer fluid's viscosity as opposed to its surface tension (Tables I and II). As fluid viscosity increased, jet and ultrasonic nebulizers exhibited contrary trends in droplet size variation in that MMDs progressively decreased with the former and increased markedly with the latter devices. Reflecting previous findings (20,21), MMDs were consistently smaller when jet nebulizers were operated at the higher flow-rate and the jet nebulizers generated aerosols with appreciably smaller MMDs (0.86–3.69 μm) than the ultrasonics (MMDs: 2.79–6.45 μm—Table I). Both ultrasonic nebulizers were unable to nebulize more viscous solutions of propylene glycol and glycerol than those specified in Table II. The Medix could nebulize the 0.65–5.0 cs silicone fluids while the Easimist could not continuously nebulize any.

Jet Nebulization. Typical findings for jet nebulization are shown by the Pari LC (Table I). The highest MMDs (3.57–2.98 μm at 6 L/min; 3.13–2.55 μm at 8 L/min) occurred with water, silicone fluid 200/0.65 cs, glycerol 10% (v/v) and ethanol. While these fluids differed markedly in their surface tension values (over a range of approximately 55 dyne/cm), they possessed the lowest viscosity values (all below 1.31 cP). By contrast, lower MMDs occurred with fluids which had higher viscosity values but comparable surface tension values. As described by previous studies (10,11) the more viscous fluids tended to produce smaller droplets. Within specific fluid systems, such as glycerol 10%–50% (v/v), propylene glycol 10–50% (v/v) and the 200 grade silicone fluids, MMDs decreased as fluid-viscosity increased. (It is noteworthy that MMD values obtained for the silicone fluid series decreased over the earlier viscosity range whilst the converse was true the more viscous fluids). In the glycerol and silicone fluid series, surface tension did not greatly alter though the effect on the MMD was considerable (3.10–2.47 μm at 6 L/min; 2.90–1.97 μm at 8 L/min: 3.34–1.17 μm at 6 L/min; 2.86–1.06 μm at 8 L/min respectively). These findings suggest that viscosity and MMD were inversely related and that surface tension did not influence the MMD value. However, when the fluid systems were analysed separately a correlation between surface tension and MMDs appeared to exist. In the glycerol and propylene glycol solutions, surface tension was directly proportional to droplet-size, whilst the converse was true for the silicone fluids. Furthermore, although the glycerol and propylene glycol series exhibited similar viscosity values, the propylene glycols possessed lower surface tension values (i.e. 62–45 dyne/cm as opposed to 73–70 dyne/cm) and produced aerosols with much smaller MMDs (circa 40%). While droplets generated

Table I. Mean Mass Median Diameter and Total Output (% of the Initial Amount Released) for a Range of Fluids Nebulized in a Pari LC Nebulizer

Fluid	Viscosity (cP)	Surface Tension (dyne/cm)	Mass Median Diameter (μm)		Total Output (%)	
			6 L/min	8 L/min	6 L/min	8 L/min
Water	1.00	72.80	3.6	3.1	74.3	75.4
Ethanol	1.19	24.10	3.0	2.5	96.6	97.3
Glycerol 10%	1.31	72.90	3.1	2.9	71.5	73.7
Glycerol 25%	2.09	72.21	2.6	2.4	68.1	72.8
Glycerol 50%	6.03	70.00	2.5	2.0	48.4	59.6
P. Glycol 10%[a]	1.50	62.00	1.9	1.6	73.2	75.7
P. Glycol 30%	3.00	52.00	1.6	1.5	70.4	72.1
P. Glycol 50%	6.50	45.00	1.3	1.2	50.8	61.6
S. F. 200/0.65 cs[b]	0.49	15.90	3.3	2.9	98.0	98.4
S. F. 200/1 cs	0.82	17.40	2.4	2.0	89.6	94.6
S. F. 200/5 cs	4.60	19.70	1.6	1.3	87.1	90.5
S. F. 200/10 cs	9.40	20.10	1.7	1.7	79.3	83.4
S. F. 200/20 cs	19.00	20.60	1.7	1.5	76.7	80.0
S. F. 200/50 cs	48.00	20.80	1.2	1.1	62.1	63.7
S. F. 200/100 cs	97.00	20.90	1.4	1.4	24.5	39.2

Each value is the mean of three experiments.
[a] P. Glycol = propylene glycol.
[b] S. F. = Silicone fluid.

Table II. Mean Mass Median Diameter and Total Output (% of the Initial Amount Released) for a Range of Fluids Nebulized in a Medix Electronic Nebulizer

Fluid	Viscosity (cP)	Surface Tension (dyne/cm)	Mass Median Diameter (μm)	Total Output (%)
Water	1.00	72.80	4.5	68.3
Ethanol	1.19	24.10	4.7	92.7
Glycerol 10%	1.31	72.90	4.4	45.7
Glycerol 20%	1.92	72.54	4.5	26.5
Glycerol 25%	2.09	72.21	4.7	19.6
Glycerol 30%	2.74	71.73	4.8	15.8
Glycerol 35%	3.36	71.32	5.3	12.6
Glycerol 40%	4.09	70.61	5.6	8.6
Glycerol 45%	4.94	70.35	6.1	8.2
P. Glycol 10%[a]	1.50	62.00	4.6	65.3
P. Glycol 30%	3.00	52.00	4.7	19.1
P. Glycol 40%	4.32	47.65	4.7	12.6
P. Glycol 45%	5.09	46.00	5.0	12.0
P. Glycol 50%	6.50	45.00	5.6	8.9
S. F. 200/0.65cs[b]	0.49	15.90	2.8	96.8
S. F. 200/1cs	0.82	17.40	2.9	93.5
S. F. 200/1 + 5cs	2.45	18.25	4.1	37.5
S. F. 200/5cs	4.60	19.70	4.8	1.5

Each value is the mean of three experiments.
[a] P. Glycol = propylene glycol.
[b] S. F. = silicone fluid.

from the Sidestream nebulizer were smaller (circa 40%) the trends were, apart from the position of the peak and trough MMDs at specific silicone fluid viscosities, generally congruent with trends obtained with the Pari LC. Aerosols from the Cirrus device displayed comparable MMDs to the Pari LC. Although many of the trends in droplet-size variation correlated with those for the Pari LC, slight differences existed. While MMDs decreased with increasing propylene glycol viscosity, similar values occurred with the 25 and 50% (v/v) glycerol solutions. For silicone fluids trough MMDs were attained at a lower viscosity (5 cs) with a subsequent increase in droplet-size for the higher viscosity members.

Ultrasonic Nebulizers. Unlike the jet nebulizers, the more viscous fluids consistently generated larger droplets with the ultrasonic devices. (Table II). Nebulization of the lower propylene glycol and glycerol solutions in the Medix Electronic gave MMDs similar to water (approximately 4.4–4.6 μm). As the content of propylene glycol was increased from 10% to 50% (v/v), the MMD values progressively increased. Marked increases occurred between the 40%–45% (v/v) and 45%–50% (v/v) solutions. The glycerol solutions behaved similarly—droplet-size increased from 4.79–6.08 μm over the 30–45% (v/v) range. Empirical formula dictate that reducing surface tension should decrease droplet-size. Although surface tension decreased by approximately 25% (for propylene glycols) or remained constant (for the glycerols), the marked increases in MMD highlighted the importance of viscosity and undermined surface tension's role in determining droplet-size. However, when the silicone fluids were considered, such relationships became more complex. MMDs for the 200/0.65 cs and 200/1 cs silicone fluids were low for ultrasonic devices (i.e 2.79 μm and 2.87 μm) and may be partly due to the exceptionally low viscosity (0.49 cP and 0.82 cP respectively) and/or surface tension (15.90–19.70 dyne/cm) of the fluids. MMD values for the other fluid tested increased with increasing viscosity, reaching 4.82 μm for the 200/5 cs fluid (4.60 cP). The Medix was unable to nebulize the higher silicone fluid members. While the low surface tensions may have therefore influenced droplet-size, the higher viscosities appear to have suppressed nebulizer operation. For instance, ethanol (with a low viscosity – 1.19 cP) was readily nebulized, despite having a comparable surface tension (24.10 dyne/cm). Generally, the data obtained for the Easimist device (though restricted to propylene glycol and glycerol solutions) correlated well with those obtained from the Medix nebulizer.

Correlation Figures. An inverse relationship between the viscosity of the nebulizer fluid and the MMD value in jet nebulizers (Fig. 1A) and a direct correlation for the ultrasonic devices (Fig. 1B) were evident. Notable changes in MMD values occurred over the viscosity range 0.5–10 cP. As the viscosity increased to approximately 10 cP, the MMD value for the three jet nebulizers at both flow rates decreased. Thereafter, droplet-size increased with increasing viscosity up to the 97.00 cP value for the Sidestream and Cirrus nebulizers and remained consistent for the Pari LC device. By contrast, higher MMD values were observed when both the Medix and Easimist devices nebulized the more viscous fluids. The relationship between surface tension and MMD was less obvious (Fig. 2A, B). When individual fluid series were examined, a direct relationship appeared to exist between surface tension and droplet-size for propylene glycol and glycerol solutions in jet nebulizers. The opposite seemed true of the silicone fluids where viscosity effects apparently dominate. In ultrasonic nebulizers, MMD and surface tension were inversely related in the case of propylene glycol and glycerol solutions and are directly related in the case of silicone fluids. However, the interplay

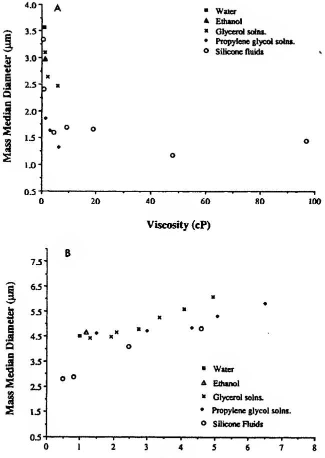

Fig. 1. Correlation plots of droplet-size (MMD) against fluid viscosity for fluids nebulized (A) in a Pari LC jet nebulizer operated at 6 L/min; and (B) in a Medix Electronic ultrasonic nebulizer operated at the mid power setting (n = 3). While the MMDs were inversely related to viscosity over the 1–10 cP range in jet nebulizers, a direct correlation existed for the ultrasonic devices.

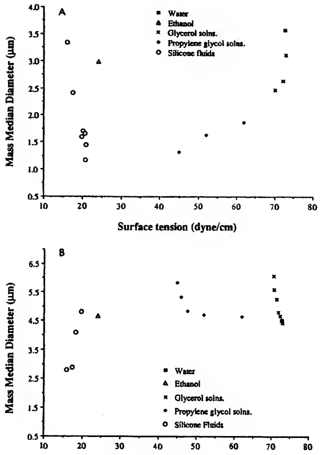

Fig. 2. Correlation plots of droplet-size (MMD) against fluid surface tension for fluids nebulized (A) in a Pari LC jet nebulizer operated at 6 L/min; and (B) in a Medix Electronic ultrasonic nebulizer operated at the mid power setting (n = 3). In jet nebulizers, while an inverse relationship existed between MMD and surface tension for silicone fluids, a direct correlation was noted for the propylene glycol and glycerol solutions. By contrast, MMD and surface tension were directly related for silicone fluids in ultrasonic nebulizers, with an inverse correlation existing for the propylene glycol and glycerol solutions.

between viscosity and surface tension may, in combination with other factors, serve to complicate data interpretation.

The MMDs were largely consistent throughout the nebulization period and tended to alter only during the "sputtering" phase. During air-jet nebulization, the temperature of the nebulizer fluid falls by approximately 10°C, primarily because outgoing air becomes saturated with solvent vapour and in ultrasonic nebulizers temperature increases by up to 15°C. Although this would normally be associated with changes in both viscosity and surface tension of the fluids, there was little variation in drop-size during the continuous phase of nebulization in the systems studied (Fig. 3).

Percentage of Droplets < µm, 90% Undersize and Size Distribution. The percentage of droplets less than 5 µm was used to define the respirable percentage. The MMD value and the % of droplets < 5 µm are inversely proportional while the 90% undersize is directly proportional to the MMD value. The results correlated well with MMD values for all three jet and both ultrasonic nebulizers. The span gives a measure of the width of the volume distribution relative to the median diameter. The heterodispersity of aerosols produced from ultrasonic nebulizers was less than those produced from jet nebulizers. All the nebulized aerosols were polydisperse with span values ranging between 1.74–5.61 for jets and 1.36–2.34 for ultrasonics. Although higher flow-rates have previously been reported to produce more heterodisperse aerosols (20), span values were not found to be consistently higher for aerosols produced at higher flow rates (8 L/min). Within specific fluid systems, trends of increased span value with decreasing MMD values were sometimes noted, particularly with the Pari LC and Cirrus but these findings were not conclusive. For the ultrasonic nebulizers studied, a good correlation existed between the physicochemical properties of the nebulizer fluid and the span. Trends of decreasing span with increasing MMD were observed for the three fluid series.

Nebulization Time and Fluid Output. When the fluid

was nebulized to dryness, nebulization time was taken as the time at which aerosol emission/detection ceased. As expected, the more viscous fluids nebulized more slowly and fluids in jet devices nebulized more quickly at the higher flow-rate. Certain fluids (ethanol, silicone fluids 200/0.65 cs to 200/10 cs) were nebulized in such a short period that the fill volume had to be increased. Nebulization times (2–8 min) were shortest for the silicone fluids 200/0.65 cs, 200/1 cs and for ethanol (irrespective of nebulizer type). Water, glycerol 10% (v/v) and propylene glycol 10% (v/v) solutions exhibited comparable nebulization times (6–16 min). The more viscous fluids required considerably longer times to nebulize to dryness, typically exceeding the predetermined maximum. After nebulization, a residual amount of fluid remains trapped on the nebulizer walls and baffles. In this study, the total output values, as a percentage of the initial amount of fluid, were calculated from simple weight measurements since inclusion of tracer compounds may have altered the physicochemical properties and there was no suitable analytical technique to measure the residual amount of these test fluids. The more viscous solutions were associated with the highest residual amounts and consequently gave the lowest output values (Tables I and II). While between 98.4–96.6% of silicone fluid 200/0.65 cs and ethanol were nebulized in jet devices, the more viscous fluids were less efficient with much larger residual amounts and exceptionally low outputs. Whilst viscosity largely explains these findings, it does not explain the anomalous position of the earlier silicone fluids (particularly 200/5 cs). Even though the 200/5 cs fluid possesses a viscosity (4.60 cP) roughly comparable to those of the higher concentration glycerols and propylene glycols (2–6 cP and 3–6.5 cP respectively), it was associated with a much lower residual amount (approximately 2 to 3 fold less). This may in part be due to the lower surface tension which facilitated a more efficient aerosol delivery.

The outputs for equivalent fluids differed markedly between the jet and ultrasonic nebulizers. The ultrasonic nebulizers were unable to efficiently nebulize viscous fluids and were associated with exceptionally low outputs. In some cases aerosol emission was poor in the initial stages while for other fluids nebulization rate appeared to be suppressed towards the end of the nebulization period. The Medix was unable to nebulize silicone fluids beyond the 200/5 cs silicone fluid (and could only aerosolise 1.5% of this fluid in 10 min). The Easimist was worse, being unable to consistently nebulize any silicone fluid for more than 5–7 sec. It is possible that surface tension may play a role here—although silicone fluid had viscosities comparable to some of the nebulized propylene glycols and glycerols, it could not operate efficiently with such a low surface tension. By contrast, jet nebulizers could nebulize 20 to 40% of even the most viscous silicone fluid studied, 200/100 cs (albeit in 20 min). Similar trends were established for both propylene glycol and glycerol solutions. Output rates from ultrasonic nebulizers often exceed those from jet nebulizers. However, the ultrasonic devices generally retained larger volumes of the test fluids than did the jet nebulizers.

Respirable Output. Respirable output was dependent upon the percentage of droplets less than 5 μm and the total output. It was consistently higher for jet nebulizers when operated at higher flow-rates. While the total output percentages were comparable for the three jet nebulizers, respirable output percentages varied. Respirable percentages were as follows: Pari LC: 6 L/min = 21.5–71.2%, 8 L/min = 34.8–77.3%; Sidestream: 6 L/min = 18.5–87.5%, 8 L/min = 29.0–91.9%; Cirrus: 6 L/min = 19.9–73.8%, 8 L/min = 27–85.0%. The Sidestream generated aerosols with higher respirable percentages than Pari LC and Cirrus which was attributable to its smaller associated MMD values. As the viscosity increased (between 0.5–10/20 cP), smaller droplets were produced (though at the expense of reduced total output). Generally, as the fluid viscosity increased, the respirable output decreased with the most obvious reduction occurring between the more viscous members of the fluid series.

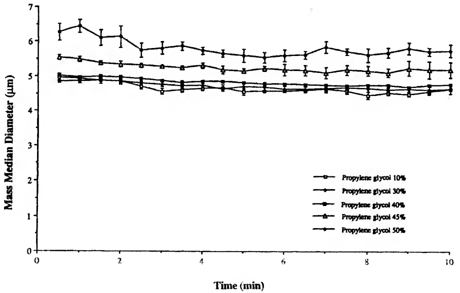

Fig. 3. The MMD (±SE) time profiles for propylene glycol solutions [10–50% (v/v)] nebulized in an Easimist ultrasonic nebulizer operated at the mid power setting for 10 min. (n = 3).

Respirable outputs for the ultrasonic nebulizers were as follows: Medix: 2.54–51.40% for non-silicone fluids, 0.79–74.21% for silicone fluids; Easimist: 2.74–39.13% for non-silicone fluids. Viscosity increases were associated with a marked reduction in MMD values and a decreased aerosol output. These acted in concert to reduce the respirable output. Consequently, the least viscous fluids produced aerosols with the highest respirable outputs.

CONCLUSIONS

In jet nebulization the droplet-size appeared to be inversely proportional to viscosity (at least between the 0.5–20 cP range), while in ultrasonic devices it was proportional to viscosity. No clear overall correlation was established between droplet-size and surface tension. The more viscous fluids required longer nebulization periods and were associated with increased residual amounts (lower outputs). While fluids of high viscosity produced aerosols with smaller MMDs in jet nebulizers, they may not be entirely suitable for clinical application due to poor patient-compliance (longer nebulization times) and low efficiency. Unlike jet nebulizers, ultrasonic devices efficiently generated aerosols (with optimum respirable output) from low viscosity fluids and indeed experienced difficulty or were unable to nebulize the more viscous fluids. Ultrasonic nebulizers were more adversely affected by variations in the physicochemical properties of nebulizer fluids than were jet nebulizers. Moreover, jet nebulizers generated an aerosol with an optimum respirable output (low MMD and high output) from median-viscosity fluids.

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PHYSICO-CHEMICAL STUDIES ON AEROSOL SOLUTIONS FOR DRUG DELIVERY I. WATER–PROPYLENE GLYCOL SYSTEMS

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SUMMARY

The aerosolization characteristics of two commercial nebulizers have been examined using propylene glycol–water systems. The output of aerosol solution droplets passed through a maximum at 30% v/v propylene glycol; however, an increased output was parallelled by an increased particle size. The quantity of aerosol solution in particles below an arbitrary therapeutic limit of 5 μm was calculated. Viscosity and surface tension were considered to be the two important physico-chemical variables that determine aerosol characteristics. The use of propylene glycol–water vehicles to deliver a dose of a test steroid is considered.

INTRODUCTION

Drugs may be administered by aerosol in a variety of disease conditions, but with few exceptions the therapy is for local rather than systemic effect. Pressure pack devices containing fluorocarbon propellants are widely employed; nevertheless, there is also interest in other forms of aerosol generation, in particular compressed air nebulizers and their use with intermittant positive pressure breathing (IPPB) machines. The present studies were prompted by the need to administer a steroidal compound to the lungs using a conventional nebulizer. The effects of formulation on the output of aerosol particles from two commercial nebulizers and the importance of the various physico-chemical factors (viscosity, surface tension, vapour pressure) have been studied. This first paper will examine water–propylene glycol systems. The second paper will consider propylene glycol–water–ethanol systems and a subsequent publication will describe the effect of relative humidity on particle size and particle deposition.

The properties of pharmaceutical aerosols have been reviewed recently by various authors (Aiache, 1973; Gorman and Hall, 1973; Greene, 1971) and the more general aspects of aerosol science may be found in the standard texts (Dautrebande, 1962; Mercer, 1973; Silverman et al., 1971). Other valuable information about the generation of

small liquid droplets is provided in chemical engineering literature under spray drying (Marshall, 1954; Masters, 1972).

An aerosol for the use in delivering drug substances to the lungs must be of a suitable particle size; however, the published literature and compendial standards are somewhat vague on this point. Most workers have taken an equivalent diameter * of 5 μm as an arbitrary therapeutic limit. Particles below this size will reach the lower airways and will be deposited, provided there is sufficient time for impaction. Very small particles will be exhaled if the subject is breathing normally; however, with the use of medication, patients are normally instructed to take and hold a deep breath. In such a situation all but the very smallest particles will be deposited.

The growth or shrinkage of liquid aerosol droplets in the lungs may be controlled by the addition of solutes that alter the vapour pressure of the system; for example sodium chloride and propylene glycol. Workers concerned with the treatment of cystic fibrosis using mist-tent therapy and administration of water aerosols have discussed such factors at length (Bau et al., 1971; Wolfsdorf et al., 1969). Propylene glycol has also been used widely in aerosol solutions for drug delivery. Dautrebande (1962) has considered the use of propylene glycol and has compared it with glycerol. He concluded that unlike glycerol, propylene glycol was not irritating and did not constrict the airways even when used undiluted with water. Propylene glycol also has the advantage of being a good solvent for a variety of drug species, especially steroidal materials.

The particle size analysis of aerosol systems may be carried out using a variety of techniques ranging from simple impactors or impingers through to laser light scattering and holography (Silverman et al., 1971). However, in all cases one is sizing the aerosol some time after it has left the atomatization device. Moreover, the sizes determined under laboratory conditions may not have direct relevance to the final sizes under the ambient conditions in the lungs.

In the present studies a cascade impactor was used to investigate the particle size distribution of water–propylene glycol aerosols.

The requirements for an aerosol solution for administering drugs using a nebulizer are as follows:

(1) good solubility of the drug in the vehicle;
(2) small dose volume; and
(3) rapid administration.

The important physico-chemical variables have been investigated using two nebulizers and propylene glycol–water mixtures from 0 to 60% v/v.

METHODS

Jet blast nebulizers. A diagram of a typical Venturi-air blast type nebulizer is given in Fig. 1. Air is blown over the top of a small capillary tube, the liquid is drawn up and is atomized. The droplets are further fragmented by baffle arrangements and a fine mist of aerosol droplets are produced from the device. Larger droplets are returned to the solu-

* The equivalent diameter of an aerosol particle would be its diameter if it behaved aerodynamically as a unit density sphere.

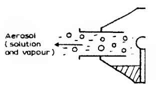

Fig. 1. Schematic diagram of

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Compressed air supply
to provide a source of
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The laboratory nitrog
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Air flow was determined
Relative humidity. Th
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Particle size analysis.
measured using a 6 stage
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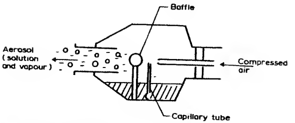

Fig. 1. Schematic diagram of Venturi-type nebulizer.

tion. With some apparatus, for example IPPB equipment, an auxiliary air flow is included.

Two different nebulizers were examined: the Maximyst (Mead Johnson Laboratories, Evansville, Ind.) and the Bird Micronebulizer (Bird Inc., Palm Springs, Calif.). The Maximyst device has a 'finger' valve for controlling air flow. The valve was closed in all experiments. The Bird Micronebulizer has provision for an auxiliary air flow when attached to an IPPB apparatus. This provision was not used and the device was operated as a closed system as shown in Fig. 1. The diameters of the capillaries were 0.50 mm for the Maximyst and 0.55 mm for the Bird Micronebulizer. In all cases the initial volume of solution placed in the nebulizer was 5 ml.

Compressed air supply. A Maximyst Air Compressor (12 psi nominal rating) was used to provide a source of compressed air. The air flow through the Maximyst and Bird nebulizers was 3.5 and 3.6 l/min respectively.

The laboratory nitrogen supply was used for studies on the effect of air pressure on nebulizer characteristics. Pressures were measured using the Bird IPPB pressure gauge. Air flow was determined by a 'Lab-crest' flow meter.

Relative humidity. The relative humidity of the laboratory varied between 40 and 50% during the period of the investigation.

Particle size analysis. The aerosol particle size and particle size distribution were measured using a 6 stage Cascade impactor (CI-6, Delron Research Products, Columbus, Ohio) (Fig. 2). The stages had been calibrated for a flow rate of 12.55 l/min. The aerosol solutions were labelled with 0.1% fluorescein (sodium salt). Fluorescein concentrations were measured with an Hitachi Spectrofluorometer (excitation wavelength 500 nm, emission wavelength 520 nm). The particle size data, expressed as cumulative percent undersize by weight, were plotted in the usual log-probability form, assuming that a log-normal distribution of particle size was present. The reproducibility between separate replicate runs were good. The mass median diameter was read off at the 50% cumulative level.

The standard deviation was determined by drawing the line of best fit through the points lying between 10 and 90% cumulative percentage and taking the ratio of the particle size at 84% to that at 50%. The quantity of aerosol that impacted in the throat arrangement (Fig. 2) was included in the calculation of cumulative weight percent values. If this contribution is ignored a smaller mass median diameter is obtained.

Concentration of aerosol in the nebulizer. During nebulization both solution and solvent vapour will be the output from the nebulizer. Consequently the concentration of drug in the solution will gradually increase. The concentration of the fluorescein label

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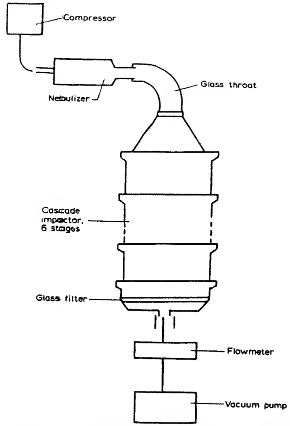

Fig. 2. Schematic diagram of apparatus for particle size analysis of aerosol particles.

was measured at the beginning and end of nebulization, as for the particle size studies above.

Replicates. In all instances at least two determinations were made on each formulation under each set of experimental conditions.

Materials. Propylene glycol from Union Carbide, Fluorescein sodium from Aldrich Chemical Company.

RESULTS

The two devices were studied using water–propylene glycol mixtures.

The factors that influence the delivery of a dose of a drug can be listed as follows:
(1) solubility of the drug in the vehicle;
(2) aerosol output (solution plus vapour);
(3) the increase in the concentration of the aerosol solution;
(4) particle size and particle size distribution; and
(5) the change in the size of the aerosol droplets after nebulization. Droplets will

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Then

$$Ct = \frac{C_0V_0 - St\,\frac{C_t + \cdots}{2}}{V_0 - (S + W)t}$$

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tion; V_0 = initial vol
and W = vapour outp
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Since $V_0 - (S + W)\,t$

where V_t is the vol
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Output of solutio
two devices is shown
similar results. There

increase or decrease in size such that the droplet exhibits a vapour pressure to match the relative humidity of ambient conditions (i.e. room or lungs).

In order to assess some of these factors the following were evaluated as indicated.

(1) Total output of aerosol (measured in microlitres of aerosol per litre of air (through jet) (μl/l). To measure this the nebulizer was weighed before and after each study and the volume determined assuming that the density of the solution did not change significantly during the experiment.

(2) Aerosol output is made up from the droplets of aerosol solution and solvent vapour that saturates the outgoing air. This loss of vapour will produce an increase in concentration of the solution in the nebulizer. This concentration effect can be considered in two parts using a drug mass balance analysis: (a) the change in volume effect due to the loss of solution and vapour; and (b) the change in total drug mass due to the loss of solution. Then

$$Ct = \frac{C_0V_0 - St\,\dfrac{C_t + C_0}{2}}{V_0 - (S + W)t} \qquad (1)$$

where C_t = concentration of solution at time t (g/ml); C_0 = initial concentration of solution; V_0 = initial volume of solution (ml); t = time (min); S = solution output (ml/min) and W = vapour output (ml/min).

Both S and W will change slightly as the solution concentrates, but for the purpose of this analysis they can be assumed to be constant if the change in volume (S + W)t is small and if C_t is only slightly greater than C_0.

$$\text{Since } V_0 - (S + W)\,t = V_t \qquad (2)$$

where V_t is the volume at time t, Eqn. 1 can be solved for S and Eqn. 2 for W.

(3) From paragraph (2) above the output of solution and vapour in μl/l or as % of total output can be calculated.

(4) Not all the aerosol solution will be effective therapeutically in the lungs. If the particle size is too large most of the solution will be deposited in the throat and the drug will be absorbed from the gastrointestinal tract and will have a systemic effect. If the particles are too small they may reach the alveolar spaces but can be exhaled again. The optimum size range for maximal local action and minimal systemic action is still the subject of dispute. A generally accepted compromise is to calculate the percentage of aerosol solution droplets below 5 μm. It must be remembered that hygroscopic particles (i.e. those containing more than 10% propylene glycol) will grow in size in the lungs under the conditions of 99% relative humidity at 37°C, below the subglottic region. The percentage of droplets below 5 μm (or any other arbitrary size) can be obtained from the data obtained with the Cascade impactor.

(5) From paragraph (4) above the output of solution (μl/l) or particles below 5 μm can be calculated.

Output of solution and vapour. The change of output of solution and vapour for the two devices is shown in Fig. 3. It can be seen that the Maximyst and Bird nebulizers give similar results. There is a maximum in the total output at around 20% propylene glycol.

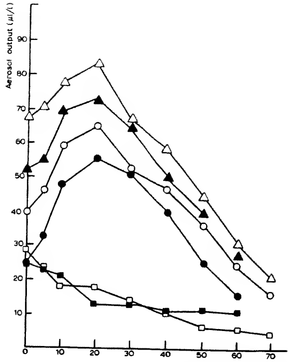

Fig. 3. Nebulization of propylene glycol solutions. The total output (△), solution (○) and vapour (□) outputs with Maximyst and (equivalent filled symbols) Bird nebulizers.

Resolution of the output data into the solution and vapour components shows the vapour output falling progressively as the propylene glycol content increases due, of course, to the effect of the glycol on the local vapour pressure of the system. The output of aerosol solution droplets passes through a maximum at 20% glycol content. The proportions of solution to vapour at any given glycol content can be calculated easily. Above 20% v/v glycol content these proportions are almost constant at 80% solution to 20% vapour. The one major difference between the two nebulizers is the quantity of aerosol lost in the 'throat' arrangement. The Bird nebulizer gives a consistently smaller loss than the Maximyst nebulizer and could be expected to give a much lower dose of the drug systemically when used clinically.

Due to the concentration effect discussed above the output from the nebulizer will not be constant with time but will change as the aerosol solution in the nebulizer concentrates. Below 20% v/v propylene glycol we would expect the output to increase with time but above 20% v/v propylene glycol the output should decrease. For example, the initial rate of output for 50% v/v propylene glycol was 42 µl/l falling to 20 µl/l at 19 min, at which time the output ceased because there was insufficient solution remaining in the nebulizer to give the capillary-Venturi effect.

Particle size analysis. Log-probability plots for 10 and 60% v/v propylene glycol solu-

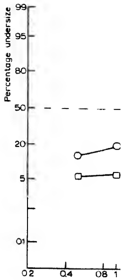

Fig. 4. Particle size analys
propylene glycol.

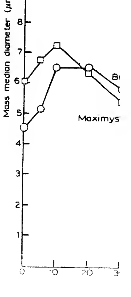

Fig. 5. Relation between
Maximyst nebulizer.

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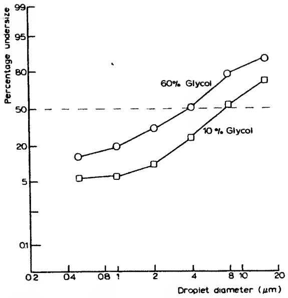

Fig. 4. Particle size analysis of aerosol droplets (log probability plot). ○, 60% propylene glycol; □, 10% propylene glycol.

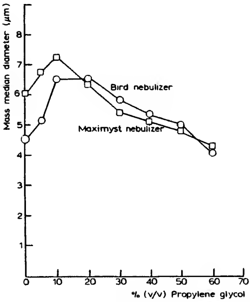

Fig. 5. Relation between aerosol particle size and propylene glycol content. ○, Bird nebulizer; □, Maximyst nebulizer.

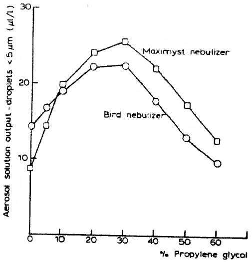

Fig. 6. Effect of propylene glycol content on the output of 'effective' aerosol droplets. ○, Bird nebulizer; □, Maximyst nebulizer.

tions are shown in Fig. 4. As the glycol content increases the mass median diameter falls and the standard deviation increases. The change in mass median diameter with the full range of propylene glycol content is shown in Fig. 5. The mass median diameter passes through a maximum at 10% v/v propylene glycol. This maximum may be an experimental artifact. Below 10% v/v propylene glycol the propylene glycol droplets are not stable and consequently they lose water until the vapour pressure is in equilibrium with the ambient conditions within the Cascade impactor and its sampling arrangement. This suggestion is substantiated by plotting the mass median diameter against surface tension. A linear relation between the two variables breaks down at 10% propylene glycol.

We conclude that the particle size of the aerosol falls as the propylene glycol content increases. The quantity of solution below 5 µm can be determined from the log-probability plots (Fig. 6). A maximum output is found at 30% v/v propylene glycol.

Drug solubility. The solubility of the drug in the vehicle can be of paramount importance and will often play a key role in the selection of the optimum delivery system. In this work we have considered a test steroid, flunisolide (Syntex Pharmaceuticals, Palo Alto, Calif.).

The solubility of flunisolide changes exponentially with propylene glycol concentration (Table 1). In the calculation of delivery times for this drug an arbitrary dose of 1 mg has been chosen. The quantity of aerosol solution containing that dose and the volume of air needed to nebulize that quantity of solution (particles below 5 µm) and the time for nebulization using the Maximyst nebulizer are given in Table 1. It is clear that the time for delivery of a given dose decreases with increase in glycol content. The over-riding factor is the solubility of flunisolide in the vehicle and the system with the maximum output of effective aerosol (30% v/v propylene glycol) is not the best for drug delivery (extrapolation of the experimental data to 70% v/v glycol content indicates that the time for

TABLE 1

NEBULIZATION OF TES
DOSE 1 mg

Propylene glycol % (v/v)	Solubility flunisolide (mg/ml)
20	0.125
30	0.25
50	1.00
60	2.00

[a] Poulson, P., personal com
[b] Assumed that quantity o
in concentration process.
[c] Airflow = 3.5 l/min.

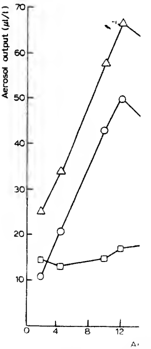

Fig. 7. The effect of air pre
put; ○, solution output; □, v

Fig. 8. Effect of air pressure

rosol droplets. o, Bird nebu-

ıss median diameter falls
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median diameter passes
may be an experimental
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It is clear that the time
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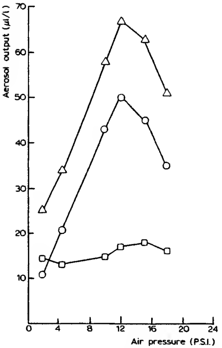
for drug delivery (extra-
icates that the time for

TABLE 1

NEBULIZATION OF TEST STEROID (FLUNISOLIDE) SOLUTION – MAXIMYST NEBULIZER – DOSE 1 mg

Propylene glycol % (v/v)	Solubility flunisolide [a] (mg/ml)	Quantity of aerosol solution (ml) required	Aerosol solution output (<5 μm) (μl/l)	Volume [b] of air (l)	Time [b] for nebulization [c] (min)
20	0.125	8	24	333	93
30	0.25	4	26	153	43
50	1.00	1	18	56	16
60	2.00	0.5	13	38	11

[a] Poulson, P., personal communication.
[b] Assumed that quantity of drug per unit time is approximately constant due to compensating effects in concentration process.
[c] Airflow = 3.5 l/min.



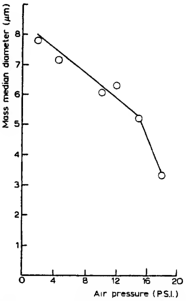


Fig. 7. The effect of air pressure on aerosol output (50% w/v propylene glycol solution). △, total output; o, solution output; □, vapour output.

Fig. 8. Effect of air pressure on particle size of propylene glycol solution aerosol droplets.

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nebulization would be about 14 min). It is concluded that 50 or 60% v/v propylene glycol will provide the best delivery system clinically if one is considering propylene glycol–water systems alone.

In the calculation of the time for dose delivery it has been assumed that the quantity of drug delivered per unit time will remain approximately constant. The increase in the concentration of the aerosol solution will produce a net reduction in output through an increased solution viscosity. However, this effect will be offset by a decreased surface tension which will favour a correspondingly larger output and also a reduction in particle size and the percentage of particles below 5 μm. In addition the nebulized solution will have increased concentration so that the dose per unit volume increases. All things considered there should be little change in the quantity of drug delivered per unit time.

The effect of air pressure. The mass median diameter for 50% v/v propylene glycol using the Bird device under continuous operation was 5 μm. However, the Bird device can be operated over a wide range of air pressures (5–40 psi) and the effect of pressure on aerosol output and particle characteristics was therefore investigated using 50% v/v propylene glycol. In these studies the output may be quoted in two ways since the airflow is not constant: μl/l as before, and μl/min.

The output of aerosol expressed as total aerosol, solution and vapour are shown in Fig. 7 and plotted as μl/l. The solution output reaches a maximum at about 12 psi and then begins to fall. The output of vapour is approximately constant when expressed as μl/l but rises gradually when expressed at μl/min.

The mass median diameter decreases with increased air pressure, reaching approximately 3 μm at 18 psi (Fig. 8). An increase in pressure also results in a more linear log-probability plot and an increased standard deviation.

The percentage of particles less than 5 μm was determined as before and the output of droplets below this size calculated. Expressing the data as μl/l indicates that the output increases in a linear manner with increased pressure until 12 psi and then levels off. However, if the data are expressed as μl/min (a more meaningful parameter for drug delivery) the relation between output and pressure is linear for all values studied. As before, the time required to give a 1 mg dose of flunisolide in 50% v/v propylene glycol can be calculated for different a[...] time.

TABLE 2

NEBULIZATION OF TEST STEROID FLUNISOLIDE SOLUTION – BIRD IPPB MICRONEBULIZER – DOSE 1 mg 50% PROPYLENE GLYCOL – 1 ml SOLUTION

Administration of particles below 5 μm

Air pressure (psi)	Time to aerosolize 1 ml 50% propylene glycol (min)
2	172
4.5	58
10	21
12	16
15	14
18	12

DISCUSSION

The output of aerc
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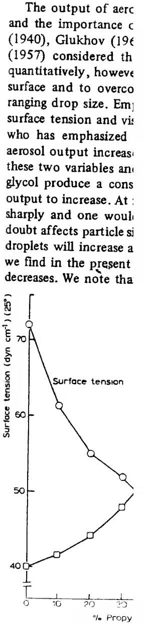

Fig. 9. Physical properties o

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nd then levels off. How-
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– BIRD IPPB MICRO-
ON

culated for different air pressures (Table 2). The higher the pressure the lower the delivery time.

DISCUSSION

The output of aerosol droplets from an atomizer is controlled by a variety of factors and the importance of surface tension and viscosity have been discussed by Abramson (1940), Glukhov (1968) and Gorman and Hall (1973) among others. Green and Lane (1957) considered that the mechanism of atomization could not easily be analyzed quantitatively, however, they pointed out that energy was required in order to create new surface and to overcome viscous forces. The Venturi-type nebulizer gave rise to a wide ranging drop size. Empirical equations have related mean droplet size to solution density, surface tension and viscosity. Similar equations have been presented by Glukhov (1968) who has emphasized the importance of surface tension. As surface tension falls the aerosol output increases. Conversely as viscosity rises output falls. The relations between these two variables and propylene glycol content are shown in Fig. 9. Small quantities of glycol produce a considerable lowering in surface tension and we would expect aerosol output to increase. At intermediate glycol concentrations the viscosity begins to rise quite sharply and one would expect the output to be decreased. This competitive effect no doubt affects particle size. Atomization theories suggest that the mean diameter of aerosol droplets will increase as the viscosity increases (Marshall, 1954, Mercer, 1973a). However, we find in the present work that as propylene glycol content is increased the mean size decreases. We note that Mercer (1973b) has commented that the effect of surface tension

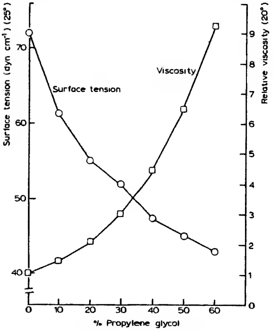

Fig. 9. Physical properties of propylene glycol solution. □, viscosity; ○, surface trension.

on the size distribution of primary aerosol droplets is not always reflected in the distribution of the final aerosol that leaves the nebulizer because of the size-selective characteristics of the nebulizer for retaining primary droplets. In agreement with our findings Searls and Snyder (1936) have reported that an increased viscosity results in a longer atomization time but the mean droplet size falls markedly.

Walkenhorst and Dautrebande (1964) measured various factors influencing the weight, number, flow rate and size distribution of the aerosol particles produced using propylene glycol systems. They noted that 50% glycol had a marked effect on the number of particles produced per ml of solution. They concluded that for their systems lowering of surface tension had no real benefit. The addition of propylene glycol did not alter either the mean size or size distribution but increased considerably the number of particles.

No doubt the exact relationship between aerosol solution output, mean particle size and viscosity and surface tension is a complex function of the design of the nebulizer and its dimensions. Of interest in the present work was a clear relation between total output and particle size. For a given atomization pressure it was found that an increased output was always at the expense of an increased particle size. Thus the net benefit in terms of particles of therapeutic importance (e.g. less than 5 μm) may be quite small.

The propylene glycol concentration for maximal output of small particles was 30% v/v; however, one must temper such an observation with the known properties of the drug molecule, in particular its solubility in the vehicle. We see clearly for the case of a test steroid that the solubility effect dominates all other considerations so that the 50–60% glycol systems provide the shorter times for administration (times too long for clinical situations). The second paper will consider propylene glycol–ethanol–water mixtures where one is able to achieve reasonable solubility of the drug in the vehicle without an unacceptably high solution viscosity.

An increased output together with a reduction in mean particle size can be achieved using an increased atomization pressure. Mercer et al. (1968) have reported similar data to those described in Figs. 7 and 8, namely a fall in particle size with increased pressure and aerosol solution output (expressed as μl/l air) passing through a maximum at 10 psi. The time to administer a dose of test drug can be greatly reduced by increasing the atomization pressure.

CONCLUSIONS

(1) There is little difference in the performance of the Maximyst and Bird nebulizers when used to nebulize propylene glycol–water mixtures.

(2) The maximum output of aerosol solution is at 20% v/v glycol.

(3) The mass median diameter of the aerosol solution reaches a maximum of 7.25 μm at 10% v/v propylene glycol. Further increase in glycol content produces a decrease in particle size.

(4) The output of aerosol solution for particles below 5 μm (a size usually accepted as the upper limit for therapeutic activity) reaches a maximum at 30% v/v propylene glycol.

(5) In delivering a dose of a test steroidal compound the solubility of the drug in the vehicle must be considered. As a consequence the optimum vehicle for drug delivery is 50 or 60% propylene glycol.

(6) An increase in
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ACKNOWLEDGEMENTS

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(6) An increase in atomization pressure gives rise to an increased output of aerosol droplets up to a maximum at 12 psi and a decreased particle size. The output of aerosol droplets below 5 μm (expressed as l/min) is linearly related to air pressure.

ACKNOWLEDGEMENTS

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Peart et al.
Serial No. 10/759,280
Filed: January 20, 2004

Confirmation No. 6861
Group Art Unit: 1616
Examiner: Alstrum Acevedo, James Henry

For: "Δ^9 *TETRAHYDROCANNABINOL (Δ^9 THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE*"

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JEFFRY G. WEERS UNDER 37 C.F.R. 1.132

Dear Sir:

1. I am currently employed by Nektar Therapeutics (formerly Inhale Therapeutic Systems, Inc.) (which has licensed the above-identified patent application), where I have been employed since 1999. I hold the position of Senior Director, Pharmaceutical Development. I am an expert in the field of aerosolized medication and have particular knowledge and understanding of hydrofluoroalkane (HFA) propellants and the formulation challenges presented in the generation of HFA based metered dose inhalers (MDIs). I have experience over the last 20+ years as Research Director in colloid-based research, including extensive experience with a wide variety of colloidal systems including: micelles, microemulsions, emulsions, liposomes, microbubbles, foams, liquid crystals, suspensions, and aerosols. I have a Bachelor of Science degree, with Honors, in Chemistry from University of Puget Sound (1980) and a Ph.D. in Chemistry from University of California at Davis (1985).

2. I have reviewed the above-identified patent application, the pending claims, the office action dated December 28, 2005 which has been entered in this application, and the references

relied upon by the Examiner for the obviousness rejections. It is my opinion that the invention, as claimed, would not have been obvious to one of ordinary skill in the art over any combination of references cited by the Examiner.

3. I am familiar with the level of skill of one of ordinary skill in the art in the field of aerosolized propellant based pharmaceutical formulations used in MDIs. Typically, the individual would have had at least a bachelor's degree in pharmaceutics, but more often he or she would have had an advanced degree such as a Ph.D. In addition, he or she would have had at least eight years hands on experience in working with propellants such as chlorofluorocarbons (CFCs) and HFAs such as 1,1,1,2-tetrafluorethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227). Furthermore, he or she would be familiar with at least some of the many articles written by Dr. P.R. Byron in such journals as *Pharmaceutical Research* and *Int. J. Pharm.*, as well as the Respiratory Drug Delivery Proceedings edited by Dr. Byron for CRC Press, Inc. One of ordinary skill in the art would recognize the many challenges that have confronted the MDI industry in view of international treaties calling for the phase out of ozone depleting propellants such as CFCs.

4. One of ordinary skill in the art would have recognized that solubilizing drugs in HFA propellants is a difficult and challenging hurdle in the preparation of acceptable MDI formulations. It would be particularly surprising and unexpected to one of ordinary skill in the art that the solubility of THC in HFA propellants is high. For example, this high solubility is particularly striking when comparing the solubility of common bronchodilators, corticosteroids and surfactants in HFA 134a. The solubility of butixocort propionate in HFA 134a is 0.02% w/w (see McNally et al. U.S. Patent 5,653,961, cited by the Examiner in the office action dated December 28, 2005); the solubility of beclomethasone dipropionate is 0.03% w/w (see Verveat et al., *Int. J. Pharm.* 186:13-30 (1999)); and the solubility of flunisolide hemihydrate is less than 0.0006% w/w. The results in HFA 227 are similar. Solubilities of surfactants in HFA propellants is detailed in Blondino et al., *Drug Dev. Ind. Pharm.* 24:935-945 (1998)). The solubility of oleic acid is less than 0.02% w/w, and of sorbitan trioleate is less than 0.02% w/w.

In order to collect reliable solubility data, one of ordinary skill in the art would know that he or she needs to wait a period of time after combining the medication with the propellant in

order to undergo dissolution and reach equilibrium. The above-identified patent application demonstrates in Table 3 that the solubility of THC in HFA propellants is an order of magnitude higher than either the hydrophobic or hydrophilic compounds quoted above, and Table 4 demonstrates that the concentration of dissolved THC remains stable for long periods of time under extreme test conditions. Prior reports have shown similar solubilities to the extremely hydrophobic THC discussed in the above-identified patent application only for hydrophilic compounds (see Blondino 1998 and Vervaet 1999). Hydrophobic compounds (e.g., butixocort) are expected to show solubilities in HFA propellant about 1/10 that which has been discovered by the inventors in THC.

5. One of ordinary skill in the art would know that in order to be a viable formulation for use in a metered dose inhaler the following criteria, among others, must be met:

A) The first option for the formulation of an MDI would be to prepare a suspension formulation (in this instance the drug would not be soluble in the propellant (e.g., HFA 134a). However, for a resinous substance such as THC which could not be processed to produce 2-3μm sized particles, suspension formulations are not an option. In this instance, solution formulations are the only option and the drug must be soluble in the propellant (e.g., HFA 134a). Furthermore, the drug must be soluble in high enough quantities that the MDI can provide therapeutically effective doses to the patient.

B) The formulation must be able to produce a significant percentage of respirable droplets when aerosolized (i.e., droplets less than 10μm in diameter).

C) The formulation must be chemically and physically stable for a significant period of time (i.e., there must be a useful "shelf-life" for the product, while still maintaining suitable aerosol characteristics).

A variety of factors impact on each of these three criteria, and if any of these factors is out of kilter, producing a viable MDI will be impossible.

6. The above-identified application would demonstrate to one of ordinary skill in the art the unexpected result that therapeutically feasible respirable doses of THC are possible in HFA propellants due to the drug's high solubility in HFA 134a and HFA 227, both of which are high vapor pressure liquified gases. While the addition of ethanol would be expected to increase THC

solubility, one of ordinary skill in the art would know that ethanol concentrations should be minimized for toxicological reasons. Thus, one of ordinary skill in the art would assume that without significant levels of solvent, not enough THC could be solubilized to provide therapeutic doses; however, the drug's newly discovered high solubility in HFAs overcomes this problem.

Respirable doses ranging from 0.25 to 1mg are believed to be necessary for THC's therapeutic efficacy in inhalation. MDI metering values usually meter by volume in the range of 25-100 µl. This corresponds to 30-120 mg of propellant. The table below shows the relationship between the needed concentration of THC in solution and the dose metered by an MDI with a 100 µl metering valve.

Concentration of THC in Solution

HFA 134a MDI	**THC Metered Dose**
0.2% w/w	0.24 mg (as can be seen from Table 3 of the application this is possible in HFA 134a alone (0% ethanol)
1.0% w/w	1.2 mg (requires less than 5% ethanol–see Table 3)
2.0% w/w	2.4 mg (requires less than 10% ethanol)
3.0% w/w	3.6 mg (requires less than 10% ethanol)
4.0% w/w	4.8 mg (requires less than 15% ethanol)
5.0% w/w	6.0 mg (requires less than 15% ethanol)

It would be clear to one of ordinary skill in the art that the results in this table which correlate to the data presented in Table 3 of the application that the high concentrations in solution that result from both the use of HFA propellants and ethanol as a co-solvent enable large metered doses of THC to be achieved. For example, from the results reported in the above-identified application, it can be seen that the solubility of THC in 5% ethanol/95% HFA 134a is 1.585% w/w and this enables an MDI with a metered dose of 1.10 mg to provide a particle (respirable) fraction of more than 20% even with a non-optimized spray nozzle.

7. For background purposes, it should be understood that one of ordinary skill in the art would know that MDIs meter fixed volumes of liquid formulations containing ingredients with

different degrees of volatility. These fixed volumes are atomized at the nozzle provided the formulation has sufficient vapor pressure. High vapor pressure MDI formulations produce smaller, more respirable aerosols (see, Moren, *Int. J. Pharm.* 1:213-218 (1978)). The liquid in the MDI occupies 95-100% of the sprayed formulation and thus it is the nature of this liquified propellant (some ingredients will vaporize on leaving the nozzle, while others will not) and the speed with which it is propelled by its own vapor that dictate the droplet size formed at the spray nozzle of the actuator (see, Polli, *J. Pharm. Sci.* 58:484-486 (1969)). Inclusion of large concentrations of surfactants or ethanol is not advisable because they create large non-respirable aerosols. For example, it is known that the use of ethanol as a co-solvent to produce drug solutions in propellants results in producing large, less respirable aerosols because of the low volatility of this co-solvent in CFC propellants (see Bell, *J. Pharm. Pharmac.* 25:32P-36P (1973)). In addition, high non-volatile drug concentrations increase aerosol size and decrease the respirable fraction of the dose (see Byron, Respiratory Drug Delivery, Chapter 7, CRC Press 1990).

THC is a high dose, non-volatile drug. Thus, a significant challenge in formulating an aerosolizable composition of THC is to minimize the concentration of non-volatile ingredients (e.g., cosolvents, surfactants) in order to maximize the respirability of the aerosol leaving the nozzle; smaller aerosols being more respirable.

8. A metered dose represents the product of the metered volume supplied by the MDI and the drug concentration in the liquified formulation. Thus, increased concentrations enabled decreased metered volumes and vice versa to achieve the same dosage. Increasing the metered volume or drug concentration tends to increase particle size of the emitted aerosol because more energy is necessary to evaporate the larger propellant volume and large drug concentrations raise the non-volatile constituent concentration and thereby the size of the resulting aerosol.

The available data on the commercially available oral form of THC, Marinol®, indicates that an administered dose of 2.5-5 mg is effective but only 10% of this dose is bioavailable or absorbed systemically. The inventors of the present application have demonstrated that THC is well absorbed following inhalation (see Lichtman, *Eur. J. Pharm.* 399: 141-149 (2000)). If it is assumed that there is 100% availability of the respirable dose (i.e., aerodynamic diameters less

than or equal to 5.8μm), then usable MDI products would need to deliver doses of 0.25-0.5 mg in one or two puffs. If there is a need for higher doses, this range might be extended to 1 mg. In 1998 and following, before this invention, metering valves for inhalation purposes ranged between 25 μl and 100 μl. Thus, the metering volume and the required respirable dose define the useable concentration range for the drug. A significant discovery reported in the above-referenced application is that the compositions will be suitable for providing THC at therapeutically effective dosages. This can be seen by the table below.

Valve Volume (μl)	Concentration (% w/w) [a]	THC Dose (mg) metered[b]; emitted[c]; and respirable[d]	Number of puffs	Total Repirable Dose (mg)
25	2% (II)	0.6;0.5;0.125	2	0.25
25	2% (II)	0.6;0.5;0.125	4	0.50
25	4% (III)	1.2;1.0;0.25	1	0.25
25	4%(III)	1.2;1.0;0.25	2	0.50
50	1% (I)	0.6;0.5;0.125	2	0.25
50	1% (I)	0.6;0.5;0.125	4	0.5
50	2% (II)	1.2;1.0;0.25	1	0.25
50	2%(II)	1.2;1.0;0.25	2	0.5
50	4% (III)	2.4;2.0;0.5	1	0.5
50	4%(III)	2.4;2.0;0.5	2	1.0
100	1%(I)	1.2;1.0[e];0.25	1	0.25
100	1%(I)	1.2;1.0[e];0.25	2	0.5
100	2%(II)	2.4; 2.0;0.5	1	0.5
100	2%(II)	2.4; 2.0;0.5	2	1.0
100	4% (III)	4.8;4.0;1.0	1	1.0
100	0.2% (IV)	0.24[f];.0.2;0.14	2	0.28

a) Roman numerals indicate likely formulations I=1.0% THC, 4.95% ethanol, 94 05%HFA 134a;

II=2.0% THC, 9.8% ethanol, 88.2% HFA 134a; III=4.0% THC, 14.4% ethanol, 81.6% HFA 134a; IV=0.2% THC, 99.8% HFA 134a (percentages are by weight throughout)

b) Metered Dose is the mass of THC delivered through the valve

c) Emitted Dose is the mass of the THC delivered through the actuator mouthpiece. Theoretical estimate assuming actuator mouthpiece retention as seen in Table 4b of the above-identified application.

d) Respirable Dose is the mass of the THC comprising droplets with aerodynamic diameters $\leq 5.8\mu m$. Theoretical estimate assuming that $\leq 5.8\mu m$ dose fraction was unchanged by drug concentration or metering volume.

e) Approximated from Table 4b of the above-identified patent application

f) ethanol free formulation containing THC at 90% of its solubility in pure HFA 134a, showing that a total respirable dose of 0.28 mg is possible given two puffs through an actuator bearing modified spray nozzle that has a smaller diameter chosen to produce smaller aerosols.

9. The above demonstrates that the compositions which have been discovered by the applicants can be used to provide effective doses of THC to a patient. There has been a long felt need for being able to provide THC to patients in a safe and efficacious manner, and the claimed products and methods satisfy that need.

The extreme hydrophobic nature of THC has been a major stumbling block in developing pharmaceutically effective formulations. Despite the considerable effort that has been dedicated to developing a medically viable THC delivery system, none of these endeavors has met with success except for orally administered THC. Marinol® (dronabinol) capsules, an oral form of THC, the chief psychoactive cannabinoid constituent of marijuana, was the only available cannabinoid for the alleviation of nausea and emesis in patients requiring chemotherapy for cancer as well as for anorexia associated with weight loss in AIDS patients. In addition, THC was believed to possess efficacy for a variety of other conditions including analgesia for chronic pain and reducing the muscle spasticity associated with multiple sclerosis. However, the pharmacokinetics of the drug profoundly limited its clinical efficacy. In particular, dronabinol undergoes extensive first-pass hepatic metabolism resulting in only 10-20% of the administered dose reaching systemic circulation (see Unimed Pharmaceutics I (20010 Product Monograph;

Marinol (dronabinol), in pp. 1-50). Moreover, the time course of dronabinol is slow with an onset of action occurring at approximately 0.5 to 1 hours and peak effects occurring at 2 to 4 hours. Importantly, the rapid onset of action is critical to controlling nausea and emesis and particularly delayed chemo-induced nausea and emesis that is not adequately controlled by standard antiemetic agents.

In contrast, the pharmacokinetics of tetrahydrocannabinol following inhalation is considerably more favorable than the oral route of administration. First pass metabolism is eliminated and the onset of action is on the order of minutes thus allowing patients to titrate their dose better than the oral route of administration. The recognition of the advantages of the inhalation route of administration over the oral route combined with the unavailability of a tetrahydrocannabinol inhalation device have led to strong public support that physicians should have the option to prescribe marijuana to relieve the suffering of seriously or terminally ill patients. Consequently, California passed a referendum in 1996 known as Proposition 215 which allows seriously ill Californians to obtain and use marijuana for medical purposes without criminal prosecution (several other states have passed similar laws).

In January 1997, the increasing public pressure to permit the use of marijuana as medicine prompted the White House Office of National Drug Control Policy to ask the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. In the report that followed, the IOM concluded that there is a therapeutic potential for cannabinoid drugs, mainly Δ^9-THC, for alleviation of chronic pain, control of nausea and vomiting, stimulation of appetite, and for the relief of muscle spasticity associated with multiple sclerosis (see Joy et al., *Marijuana and Medicine*, National Academy Press 1999, Washington, D.C.). However, the report also acknowledged that the oral route of administration hampers the effectiveness of THC because of the slow absorption and the patient's desire to better control dosing. In addition, the report cautioned that marijuana is a crude THC delivery system that simultaneously delivers harmful chemicals in addition to THC. Thus, IOM recommended the development of rapid-onset, reliable and safe delivery THC delivery systems.

Despite the fact that the interest in THC dates back nearly thirty years when efforts were

focused on developing a CFC propellant MDI to deliver THC to the lungs for treating asthma, no acceptable delivery systems of inhalation THC have been developed. The invention described in the above-identified application provides a formulation which allows efficacious doses of respirable THC to be delivered in accurate and reproducible fashion, and with no significant degradation of the drug occurring following storage in extreme conditions. As such, it represents an important solution to a long felt and complex problem, and is surprising in view of the failures of CFC based solutions.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jeffry G. Weers

27 Mar 06
Date